Fractions 21–25 afforded a slightly yellowish compound (35 mg), mp 123–125°; $[\alpha]_D^{25}$ +27° (c 0.15, methanol); λ_{max} (methanol): 231 (log ϵ 4.60), 275 (4.14), 285 (4.13), and 295 (sh) (4.10) nm; ν_{max} (KBr): 2940, 2840, 1690, 1650, 1600, 1500, 1450, 1415, 1340, 1280, 1270, 1200, 1190, 1120, 1070, 1025, and 820 cm^{-1}; NMR: δ 2.32 (s, 3H, N-2 NCH_3), 3.05 (s, 3H, N-2' NCH_3), 3.68 (s, 3H, OCH_3), 3.75 (s, 6H, 2-OCH_3), 3.83 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 7.10–8.00 (m, 9H, ArH), and 10.00 (s, 1H, ArCHO) ppm; mass spectrum: M^+ *m/e* 666 (1), 411 (100), 256 (26), 241 (1), 206 (4), and 204 (3).

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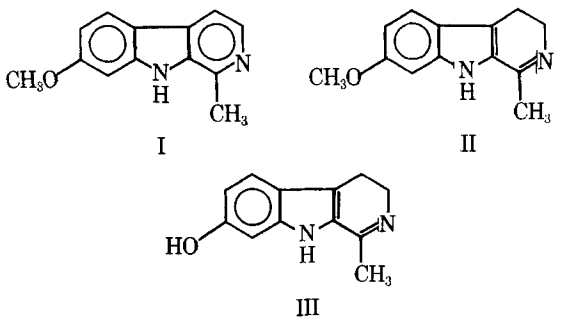
Cardiovascular Actions of Three Harmala Alkaloids: Harmine, Harmaline, and Harmalol

DARRYL H. AARONS, G. VICTOR ROSSI, and RAYMOND F. ORZECHOWSKI ˣ

Abstract □ Each of three harmala alkaloids, harmine, harmaline, and harmalol, decreased heart rate and increased pulse pressure, peak aortic flow, and myocardial contractile force in intact normotensive anesthetized dogs. Harmine reduced systemic arterial blood pressure and total peripheral vascular resistance; harmaline-evoked decreases were frequently followed by a secondary increase; and the effects of harmalol on these two parameters were inconsistent. A direct negative chronotropic effect of harmala alkaloids was suggested by observations of bradycardia in the isolated perfused rat heart and in the intact dog; neither vagotomy nor atropinization affected harmala alkaloid-induced bradycardia in the dog. Reduction in femoral vascular resistance by the alkaloids was not apparently due to activation of cholinergic, β-adrenergic, or histaminic (H_1) receptors.

Keyphrases □ Alkaloids, harmala—cardiovascular activity in dogs □ Harmine—cardiovascular activity in dogs □ Harmaline—cardiovascular activity in dogs □ Harmalol—cardiovascular activity in dogs □ Cardiovascular activity—three harmala alkaloids in dogs

Although the seeds of *Peganum harmala* have been used for centuries as a folk medicine, the harmala alkaloids continue to be of interest because of the effects they elicit on the central nervous system (CNS) and the cardiovas-



I II III

cular system. Among their pharmacological actions are a central tremorigenic action (1, 2), behavioral effects including hallucinogenesis (3), hypothermia (4), monoamine oxidase inhibition (5), and cardiovascular alterations, notably hypotension, bradycardia, and cardiac arrhythmias (6–8).

Studies of the harmala alkaloids have largely focused on their CNS effects; relatively little information exists on their cardiovascular actions. This investigation compared the cardiovascular pharmacodynamics of three major harmala alkaloids, *i.e.*, harmine (I), harmaline (II), and harmalol (III).

EXPERIMENTAL

Cardiovascular Actions in Intact Anesthetized Dogs—Mongrel dogs, 5.5–12 kg, of either sex were anesthetized with a barbiturate–urethan combination[1] (0.6 ml/kg iv). Arterial blood pressure was measured from a cannulated femoral artery[2]. Mean arterial blood pressure was derived as diastolic pressure plus one-third of pulse pressure. Heart rate was obtained from lead II electrocardiogram (ECG) tracings.

Animals were respired artificially *via* a tracheal cannula with a respirator[3]. Myocardial contractile force was recorded with a strain-gauge arch[4] sutured directly to the surface of the right ventricle (9). Aortic blood flow was measured with an electromagnetic flow probe positioned around the root of the aorta and connected to a flowmeter[5]. Total peripheral vascular resistance was calculated as the ratio of mean arterial blood pressure (millimeters mercury) to cardiac output (milliliters per minute). Recordings were made on a polygraph[6].

Each alkaloid was administered intravenously *via* a cannulated femoral vein to separate groups of dogs at increasing doses of 1, 2, 4, and, in some cases, 8 mg/kg; 60 min separated successive doses. Alkaloids were dissolved in 0.9% saline; each dose, contained in a 2-ml volume, was infused slowly over 2 min. Control dogs received 2 ml of 0.9% saline at equivalent time intervals.

Femoral Vascular Resistance Studies in Dogs—Blood from the right carotid artery of anesthetized dogs was shunted *via* polyethylene tubing[7] into the right femoral artery. The rate of blood flow into the leg was regulated by a constant-flow pump[8]. Femoral perfusion pressure was measured from a "T" connection in the tubing on the outflow side of the pump. Blood flow was adjusted so that perfusion pressure was approximately equal to systemic blood pressure recorded directly from the left femoral artery. Drugs were injected intraarterially into the perfusion circuit *via* a small section of rubber tubing interposed between two portions of the polyethylene shunt. Heparin, 5 mg/kg iv, was administered as the anticoagulant.

In one series of experiments, the alkaloids were administered directly into the blood entering the femoral artery in doses of 0.016–4.0 mg. Each dose was injected twice, consecutively, in 0.1–0.2 ml of 0.9% saline. The order of administration of the three alkaloids, as well as the order of the various doses, was randomized. Histamine and levarterenol were injected intraarterially to test the responsiveness of the experimental system. Equivalent volumes of 0.9% saline were injected for control purposes.

In a second group of experiments, the harmala alkaloids were injected twice before and at least once after administration of a pharmacological antagonist: atropine (0.5–1.0 mg/kg), propranolol (0.2–0.6 mg/kg), or brompheniramine (5.0 mg/kg) in 2 ml of 0.9% saline given by intraarterial injection over 1 min. To confirm that the antagonist produced effective blockade, a corresponding agonist (*i.e.*, acetylcholine, 2.5–5.0 μg; isoproterenol, 0.4–5.0 μg; or histamine, 5.0–10.0 μg) was injected before and after administration of the blocking agent.

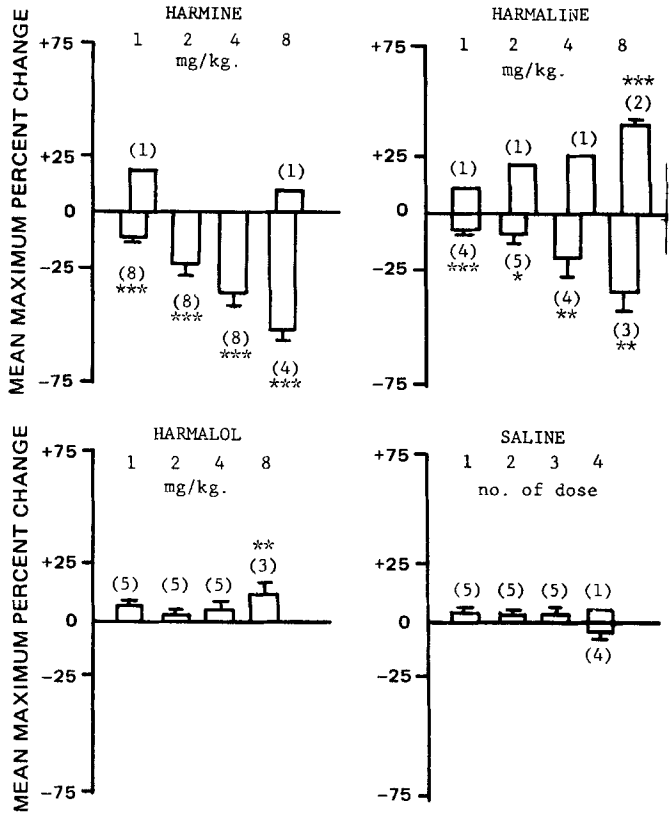


Figure 1—*Effects of intravenously administered harmala alkaloids on mean arterial blood pressure in anesthetized dogs. Key: The bars directly above and below each other indicate that opposing responses were observed in different animals receiving the same dose. Bars that overlap at the zero axis indicate that biphasic responses were observed in some animals. The sequence of the overlap indicates the order of the drug response. Numbers in parentheses refer to the number of responses comprising each mean value. Vertical lines indicate standard errors, and the level of significance is shown by the asterisks as follows:* *, $p \leq 0.05$; **, $p \leq 0.01$; *and* ***, $p \leq 0.001$.

The dose of each harmala alkaloid varied among experiments but was constant in a given animal; the dose selected was sufficient to cause a moderate (15–48%) change in femoral perfusion pressure without affecting systemic arterial pressure. Dose ranges were: harmine, 0.25–1.0 mg; harmaline, 0.25–1.0 mg; and harmalol, 1.0–4.0 mg.

Isolated Perfused Rat Hearts—The heart isolated from an adult rat was attached to a coronary perfusion apparatus[9] and perfused with Krebs–Henseleit solution aerated with 5% CO_2–95% O_2 and warmed to 38° (10). Force of contraction and heart rate were recorded with a myograph transducer[10] attached to a clamp at the apex of the heart. Initial resting tension was adjusted to 5 g. The harmala alkaloids, 0.031, 0.063, 0.125, and 0.25 mg in 0.1 ml of 0.9% saline, were introduced into the perfusate as it entered the heart. Each heart received only one alkaloid; each compound was tested in four isolated hearts. A separate group of five hearts received a series of 0.9% saline doses.

The drugs used were harmine hydrochloride hydrate, harmaline hydrochloride dihydrate, harmalol hydrochloride[11], acetylcholine chloride, atropine sulfate, brompheniramine maleate[12], histamine diphosphate, isoproterenol hydrochloride, levarterenol hydrochloride, and propranolol hydrochloride[13]. Doses of all drugs are expressed as their respective salts.

[1] Dial-Urethane, Ciba-Geigy Laboratories.
[2] Statham pressure transducer model P23AC.
[3] Harvard Apparatus.
[4] Walton-Brodie.
[5] Biotronix model T-BL 610.
[6] Grass Instrument model 5.
[7] PE240.
[8] Sigmamotor model T-8.
[9] Anderson, Metro Scientific.
[10] Narco Biosystems Linear Core F-50.
[11] Aldrich.
[12] A. H. Robins.
[13] Ayerst Laboratories.

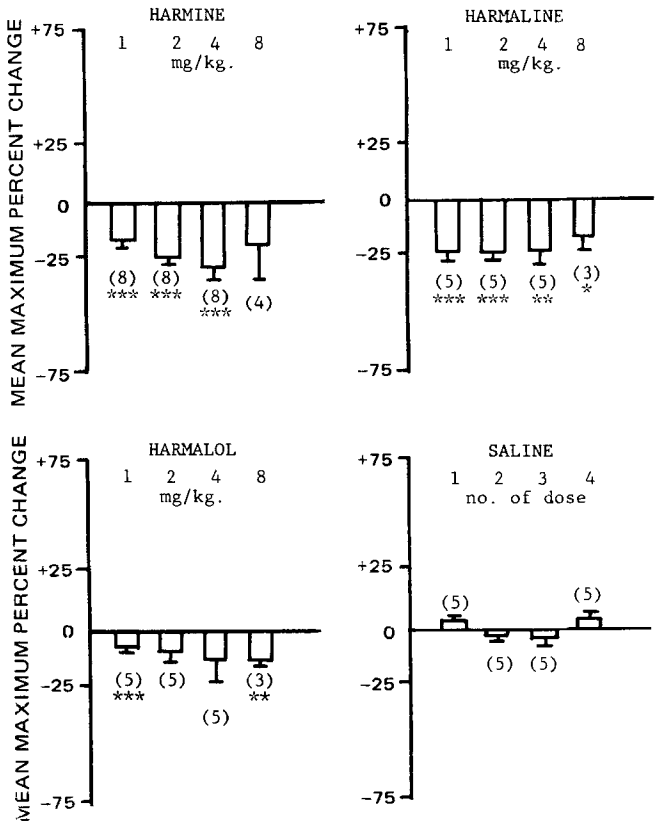


Figure 2—*Effects of intravenously administered harmala alkaloids on heart rate in anesthetized dogs. Key: see Fig. 1.*

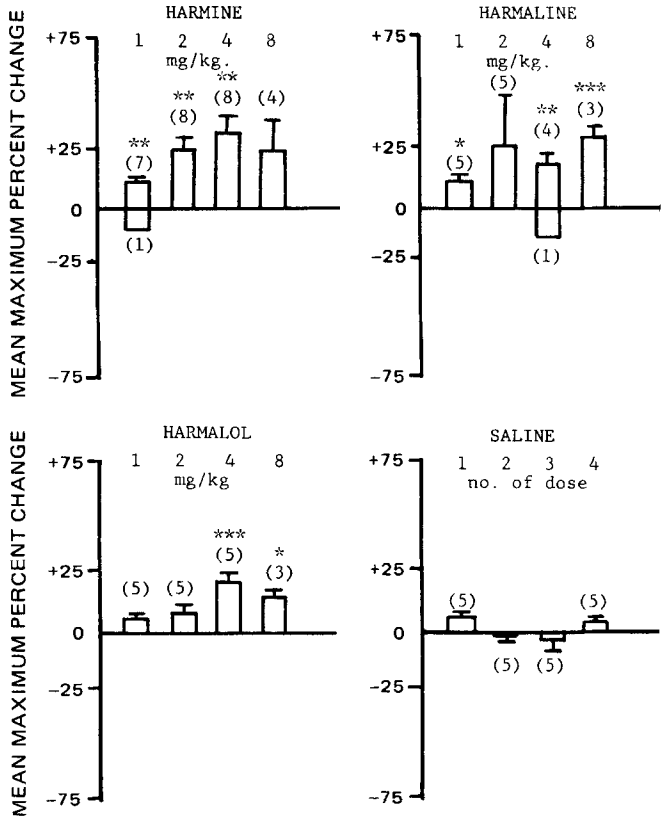


Figure 3—*Effects of intravenously administered harmala alkaloids on peak aortic flow in anesthetized dogs. Key: see Fig. 1.*

The purity of the harmala alkaloids, as assessed by TLC and NMR spectra, indicated that no significant contaminants were present.

RESULTS

Cardiovascular Effects in Intact Dogs—Harmine produced a consistent dose-related reduction in mean systemic arterial pressure in doses of 1–8 mg/kg iv; harmaline evoked similar hypotension, although less consistently and with a tendency for a secondary hypertensive response; harmalol produced variable and insignificant effects on arterial pressure at these doses (Fig. 1). Since diastolic pressure was reduced to a greater extent than systolic pressure, pulse pressure was usually increased. These effects occurred immediately after alkaloid administration and persisted from 2 to 20 min.

Bradycardia was produced by each harmala alkaloid (Fig. 2). Harmine and harmaline exhibited similar potencies, whereas harmalol was less active. The onset of heart rate reduction was immediate, and the duration was generally longer than the blood pressure changes.

Peak aortic flow was increased by all three alkaloids (Fig. 3). The smallest increase was obtained with harmalol; harmine and harmaline produced approximately equal responses. Mean aortic flow was elevated only by harmine; variable responses were elicited by harmaline and harmalol.

All three alkaloids produced significant dose-related increases in myocardial contractile force (Fig. 4). Maximum increases in contractile force usually occurred after the peak change in blood pressure.

Harmine produced a consistent and dose-related reduction of total peripheral vascular resistance. A biphasic response pattern occurred with harmaline, and harmalol produced inconsistent effects.

Cardiac arrhythmias were detected in four of seven dogs receiving harmaline and harmalol but not harmine. The dysrhythmias identified included atrial fibrillation and flutter, premature ventricular contractions, and heart block in addition to unidentified bizarre alterations. Arrhythmias were observed at various dosage levels and lasted for up to 1 hr. Elevation of the T wave of the ECG was observed with harmine (five of eight dogs), harmaline (five of seven dogs), and harmalol (one of seven dogs).

Vagotomized or Atropinized Dogs—Neither bilateral cervical vagotomy nor pretreatment with atropine antagonized the effects of harmine on heart rate and arterial blood pressure in anesthetized dogs (n = 4) (Fig. 5). The responses to harmine were essentially identical before and after doses of atropine that effectively blocked the cardiac and blood pressure changes induced by test doses of acetylcholine.

Femoral Vascular Resistance in Dog Hindlimbs—Harmine, harmaline, and harmalol, in doses of 1×10^{-4}–1×10^{-2} mmole, each reduced femoral vascular resistance (Fig. 6). The potencies of harmine and harmaline were similar, whereas harmalol was four to eight times less potent. Prior administration of atropine, propranolol, and brompheniramine did not inhibit significantly the reduction in perfusion pressure induced by harmine, harmaline, or harmalol (n = 4 in each antagonist–alkaloid series).

Isolated Perfused Rat Hearts—Each harmala alkaloid produced a dose-related slowing of the isolated rat heart (Fig. 7). The decreases observed with harmine and harmaline were approximately equal; harmalol produced a lesser reduction. A dose-related reduction in the force of contraction of isolated hearts was observed with harmine at doses of 0.031 mg and greater; variable responses were produced by harmaline and harmalol (Fig. 8).

DISCUSSION

Certain similarities, as well as distinct differences, in the cardiovascular responses to the three structurally related harmala alkaloids were observed in anesthetized dogs (Table I). Qualitatively similar responses were produced by each alkaloid on heart rate, myocardial contractile force, peak aortic flow, and pulse pressure. The most striking similarities were seen with respect to their effect on the heart. Each alkaloid reduced cardiac rate and increased myocardial force; harmine and harmaline were essentially equivalent while harmalol was less active. This finding agrees with the previous finding (11, 12) that a methoxy group on the indole nucleus (harmine and harmaline but not harmalol) enhanced the ability to reduce heart rate. Because of the rapidity of onset and relatively brief duration of the cardiovascular effects, these actions apparently are unrelated to the monoamine oxidase inhibiting properties of the harmala alkaloids. A similar conclusion was drawn by Goldberg and Sjoerdsma (7) in their report of the cardiovascular properties of several monoamine oxidase inhibitors.

Significant increases in myocardial contractile force were produced by the three alkaloids. In contrast, harmine and harmaline were reported to exert a negative inotropic effect in the anesthetized dog (7). The reason for this discrepancy is not apparent.

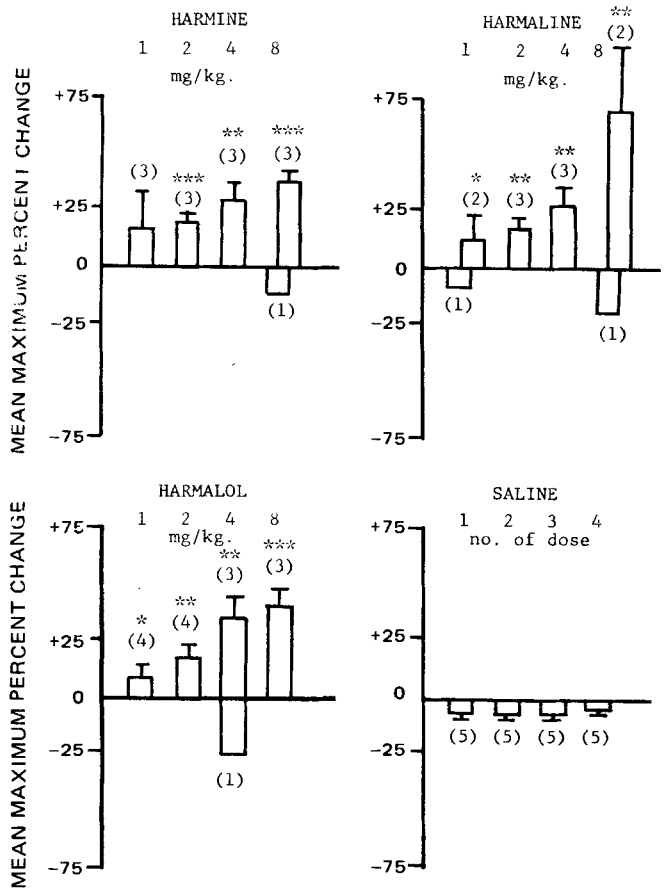


Figure 4—*Effects of intravenously administered harmala alkaloids on myocardial contractile force in anesthetized dogs. Key: see Fig. 1.*

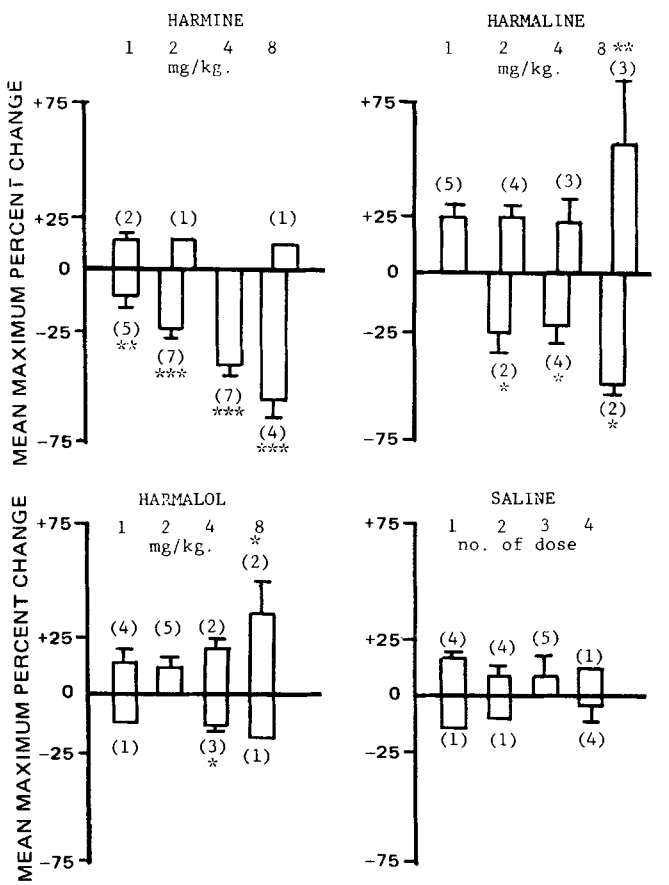


Figure 5—*Effects of intravenously administered harmala alkaloids on total peripheral vascular resistance in anesthetized dogs. Key: see Fig. 1.*

Differences among the harmala alkaloids were noted in their effects on blood pressure and total peripheral vascular resistance. The hypotensive response to intravenous administration of harmine and harmaline is in agreement with previous studies conducted in anesthetized animals and nonanesthetized humans (6–8, 11, 13). Reduction in diastolic blood pressure was primarily responsible for the hypotensive action of harmine and harmaline. Schmitt *et al.* (13) reported a similar finding in dogs receiving harmaline.

Although peak aortic flow and myocardial contractile force were increased by harmine and harmaline, minimal elevations in systolic blood pressure were occasionally observed after low doses (1 and 2 mg/kg) of these alkaloids. Higher doses predominantly reduced systolic pressure. Since the reduction in diastolic pressure was greater than that of systolic pressure, an increase in pulse pressure was obtained. Harmaline-induced reductions in mean arterial, systolic, and diastolic pressures were frequently followed by a secondary increase. This biphasic response did not occur with harmine. Harmalol had no effect on, or produced only a slight increase in, blood pressure.

Calculated values of total peripheral vascular resistance reflect changes produced by harmine and harmaline that were directionally similar to changes in systemic arterial pressure. A dose-related decrease in total peripheral resistance was produced by harmine. A biphasic response, consisting of an initial decrease frequently followed by a secondary increase, was noted with harmaline. Variable changes were produced by harmalol.

These studies demonstrated that structural variations among the harmala alkaloids result in differences in cardiovascular activity. Reduction of harmine to harmaline (dihydroharmine) had little or no effect on primary cardiovascular responses. With the exception of mean aortic flow, each parameter was initially affected similarly by the two alkaloids. This structural change, however, appeared related to secondary responses in total peripheral resistance and systemic blood pressure observed frequently with harmaline. With harmalol, in which a 7-hydroxy group replaces the 7-methoxy group of harmine, quantitative differences were seen in the effects on heart rate and peak aortic flow, while total peripheral resistance and mean systemic blood pressure differed qualitatively.

Harmaline and harmalol frequently produced cardiac arrhythmias. Although harmine did not evoke dysrhythmias in this study, it was reported previously (8) to induce ventricular arrhythmias in the cat, which were not eliminated by bilateral vagotomy or atropinization.

The negative chronotropic effect of the harmala alkaloids suggested the possibility of a parasympathomimetic mechanism. Slotkin and DiStefano (8) reported that bradycardia produced by harmaline in cats was eliminated by vagotomy. In the present study, neither bilateral vagotomy nor atropinization significantly influenced the chronotropic effect of the harmala alkaloids in dogs. Furthermore, a negative chronotropic effect was evident in the isolated rat heart, a preparation devoid of neurally mediated influences. These data do not support the possibility of a cholinergic mechanism in the cardiac slowing effect of the harmala alkaloids.

Zetler *et al.* (11) reported similar findings with harmine and harmane

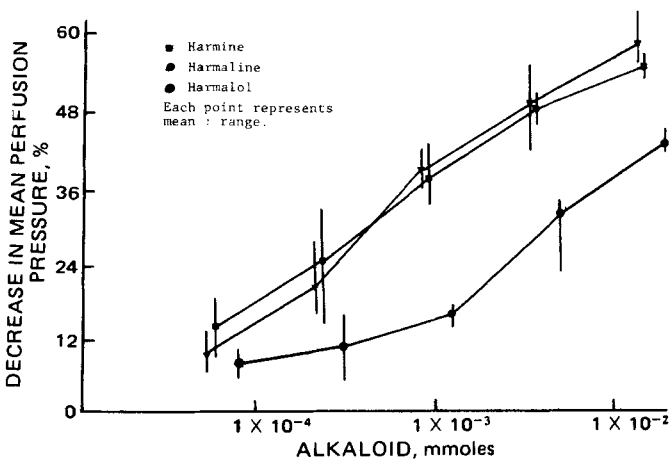


Figure 6—*Effects of three harmala alkaloids on perfusion pressure in the perfused hindlimb of dogs.*

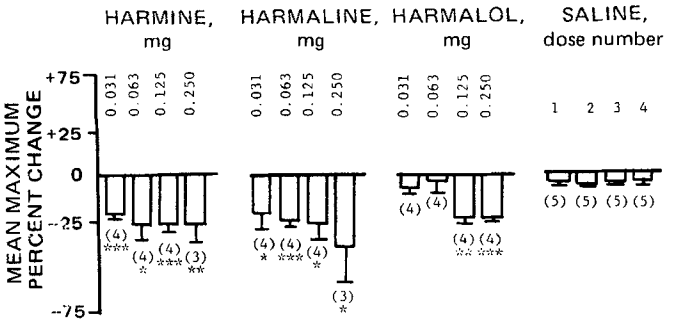


Figure 7—*Effects of three harmala alkaloids on heart rate in perfused isolated rat hearts. Key: see Fig. 1.*

in intact guinea pigs and on isolated guinea pig atria. Harmine has been reported to increase the functional refractory period of isolated guinea pig atria, but it was without effect on papillary muscle (14). Thus, cardiac slowing may result from a prolongation of the atrial refractory period.

The consistent dose-related increase in myocardial contractile force elicited in intact dogs by the three harmala alkaloids was not observed in the isolated rat heart preparation. Harmine induced a dose-dependent reduction in the force of the isolated heart, and variable responses were produced by harmaline and harmalol. Maximal increases in cardiac contractile force occurred in the intact dog after the peak effects on systemic blood pressure. Although the effects on blood pressure varied, the direction and magnitude of the responses produced by each alkaloid on myocardial contractile force were similar. This result suggests that a reflex mechanism secondary to changes in systemic blood pressure may not be responsible for the increase in contractile force. Harmine was reported to reduce myocardial contractility in the isolated guinea pig atrium driven electrically at 3/sec but to elicit a positive inotropic effect in the atria driven at a lower frequency, *i.e.*, 1/sec (15, 16). It was concluded that the positive inotropic effect of harmine, characterized by tachyphylaxis and antagonized by reserpine and propranolol, was mediated by release of endogenous norepinephrine (15, 16).

In the perfused hindlimb preparation in dogs, harmine, harmaline, and harmalol each decreased femoral vascular resistance at intraarterial doses insufficient to alter systemic arterial pressure. The nature of the vascular response to the harmala alkaloids suggested possible activation of cholinergic, β-adrenergic, or histaminergic (H_1) receptors. However, failure of specific pharmacological antagonists (atropine, propranolol, and brompheniramine) to inhibit the effect of the alkaloids on femoral vasculature eliminated involvement of the corresponding receptors. Additional evidence against a parasympathomimetic mechanism was failure of atropine or bilateral vagotomy to block the hypotensive response to harmine in intact dogs. Slotkin and DiStefano (8) reported similar results in studies with cats. Thus, vasodilation may be due to direct relaxation of vascular smooth muscle or activation of other receptor types [*e.g.*, serotonergic and histaminergic (H_2)] by harmine.

Harmaline-induced hypotension and reduction in total peripheral resistance were occasionally followed by a secondary elevation. This biphasic pattern was not observed with either harmine or harmalol. These secondary effects may result from a reflex vasoconstriction triggered in response to the fall in systemic blood pressure produced by harmaline. Support is offered by the fact that only monophasic responses were seen in the localized femoral artery preparation, in which systemic pressure was not altered. However, this finding fails to explain why harmine-induced decreases in systemic pressure did not initiate a secondary increase.

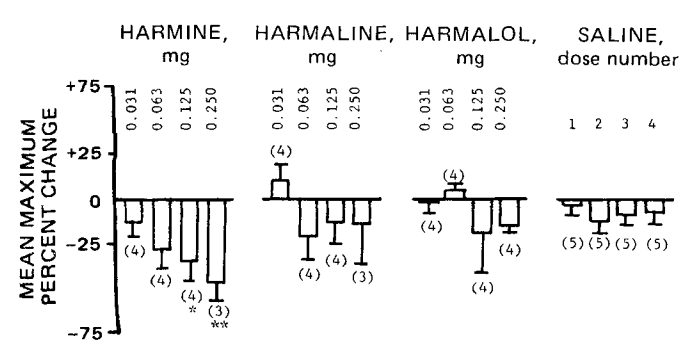


Figure 8—*Effects of three harmala alkaloids on myocardial contractile force in perfused isolated rat hearts. Key: see Fig. 1.*

Table I—Results of the Cardiovascular Analysis in Intact Anesthetized Dogs [a]

Parameter	Harmine	Harmaline	Harmalol
Mean blood pressure	− −	−−/(++)	+
Pulse pressure	++	++	++
Heart rate	− −	− −	−
Peak aortic flow	++	++	+
Mean aortic flow	++	±	±
Myocardial contractile force	++	++	++
Total peripheral vascular resistance	− −	−−/(++)	±

[a] + or − = average response less than 20%, ++ or −− = average response greater than 20%, ± = variable response, ( ) = inconsistent response, and / = biphasic response.

It is conceivable that, in addition to a relaxant effect, harmaline may activate "receptors" that produce a more prolonged vasoconstrictive response. Experimental results suggest that the vasoconstrictor component had a lower threshold of activation than did the vasodilator action. An increase in total peripheral resistance was observed in all animals receiving 1 mg of harmaline/kg.

At higher doses, both receptor types would be activated. In situations where the relaxant effect terminated before the constrictive action, a biphasic response would result. The possibility of opposing dual actions is strengthened by the fact that the effects of harmaline on mean, systolic, and diastolic pressures were less than those produced by harmine. Summation of the two opposing actions would result in a net response that was less intense than would be observed if either was unopposed.

Since anesthetics may alter neural cardioregulatory mechanisms, interpretation of the cardiovascular effects of the harmala alkaloids may have been confounded by the anesthetic agent. Cardiovascular responses in nonanesthetized animals and humans may, at least in part, be the result of a CNS action of the harmala alkaloids (17). Pressor effects of harmine in unanesthetized dogs and sheep were not blocked by atropine, suggesting that this activity is not due to cholinergic activation of the ascending reticular formation (17). Further studies are needed to delineate possible central mechanisms of the harmala alkaloids in the conscious subject.

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