concluded from the values of K_{AB} and percent biophasic availability listed in Tables II and III that it is opposite to that expected on the basis of this consideration alone. The increased percent biophasic availability observed at pH 5.0 as equal to 73.8%, relative to 43.3% at pH 7.4, may be speculatively attributed to the interaction of tropicamide cations with anionic binding sites affixed to the colloids composing the corneal tissue; the tissue binding of the drug may function to retard peripheral drug loss relative to transcorneal absorption and provide a reservoir for the drug from which it may be subsequently more efficiently biophasically available. A similar mechanism was found responsible for the pH-enhanced effectiveness of procaine as a corneal anesthetic (1). The small magnitude of the effect of administering the drug at 5.0 relative to 7.4 may be a consequence of the dilution of the unbuffered pH 5.0 vehicle with lacrimal fluid, causing its rapid buffering to a physiological pH of 7.4.

SUMMARY AND CONCLUSIONS

A basis for the resolution of the rates and relative amounts of ophthalmically administered tropicamide which are transcorneally absorbed and peripherally dissipated by other routes has been described and applied using temporal pharmacological data. The previously established kinetic indistinguishability of the biophase and systemic compartments permitted the resolution to be accomplished despite the absence of a detectable mydriatic effect in the control eye. The biokinetic analysis of the pharmacological results permitted the mydriatic behavior of tropicamide to be described in terms of quantitative parameters. Although an insufficient number of replications (four replications on each of five ophthalmic solutions) was performed to draw firm, statistically based, conclusions regarding the effects of vehicle pH, the present study does exemplify a quantitative approach to the evaluation and design of ophthalmic drug vehicles.

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Cardiovascular Effects of Bulbocapnine

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Abstract □ Upon intravenous injection of bulbocapnine into the dog, myocardial ventricular contractile force was altered and the mean arterial blood pressure was markedly lowered. Following a 50-mg./kg. dose of bulbocapnine, the blood pressure and contractile force effects of 5-hydroxytryptamine became negligible. Injections of norepinephrine, epinephrine, and isoproterenol in doses of 1 mcg./kg. and of ethylnorepinephrine in a dose of 50 mcg./kg. showed reduced effects on mean arterial blood pressure and contractile force. The effects of none of these were reversed by bulbocapnine. Animals treated with bulbocapnine, 25 mg./kg. i.p. for 5 days, became more sensitive to injections of 5-hydroxytryptamine, norepinephrine, epinephrine, and isoproterenol, as was seen in consistently altered diastolic blood pressure and contractile force effects.

Keyphrases □ Bulbocapnine—cardiovascular effects, dogs □ Catecholamine cardiovascular activity—bulbocapnine effect □ 5-Hydroxytryptamine cardiovascular activity—bulbocapnine effect

This investigation examines the changes produced in some of the cardiovascular responses of 5-hydroxytryptamine and representative catecholamines in the dog following treatment with bulbocapnine, an alkaloid, 3,4-methylenedioxy-6-apomorphine, found in the tubers of *Corydalis cava* (1). The use of the last-named agent was of interest following the reports of Walaszek and Chapman (2) that bulbocapnine depresses

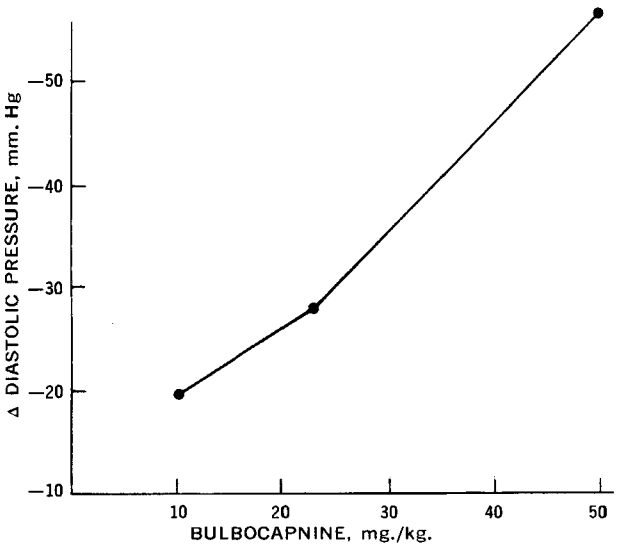

Figure 1—*Blood pressure responses to bulbocapnine. Key:* ●, *diastolic change.*

the hypertensive response to norepinephrine and reverses the response to epinephrine in cats and dogs. These authors classified the alkaloid as an α-blocking agent, using the terminology of Ahlquist (3). Since the

Table I—Drug Combinations and Doses Used

Drug or Combination	Dose	No. of Dogs
Series 1[a]		
Bulbocapnine	10 mg./kg.	5
	25 mg./kg.	5
	50 mg./kg.	5

Series 2[a]

Control Agents and Dose	Followed by Bulbocapnine, 50 mg./kg.	Followed by Challenging Agent and Dose	No. of Dogs
5-Hydroxytryptamine, 5, 10, 15, or 20 mcg./kg.	↓	5-Hydroxytryptamine, 5, 10, 15, or 20 mcg./kg.	6
Norepinephrine, 1 mcg./kg.	↓	Norepinephrine, 1 mcg./kg.	6
Epinephrine, 1 mcg./kg.	↓	Epinephrine, 1 mcg./kg.	6
Isoproterenol, 1 mcg./kg.	↓	Isoproterenol, 1 mcg./kg.	6
Ethylnorepinephrine, 50 mcg./kg.	↓	Ethylnorepinephrine, 50 mcg./kg.	6

Series 3[a,b]

	Dose	No. of Dogs
Chronic bulbocapnine	50 mg./kg.	6
Followed in separate random steps by:		
5-Hydroxytryptamine	5, 10, 15, or 20 mcg./kg.	
Norepinephrine	1 mcg./kg.	
Epinephrine	1 mcg./kg.	
Isoproterenol	1 mcg./kg.	
Ethylnorepinephrine	50 mcg./kg.	

[a] The responses measured were mean arterial blood pressure (systolic + diastolic/2) or diastolic pressure, contractile force, electrocardiogram, serum and tissue potassium. [b] Followed in all experiments by a 25-mg./kg. i.v. dose of bulbocapnine. 5-Hydroxytryptamine, norepinephrine, epinephrine, isoproterenol, and ethylnorepinephrine in doses mentioned above, respectively.

same authors reported that bulbocapnine also potentiates some of the actions of histamine (4), it was useful to check further on its relationship with various amines. The responses produced by the interactions of these agents may increase understanding of the mechanism of action of bulbocapnine. They may also elucidate the

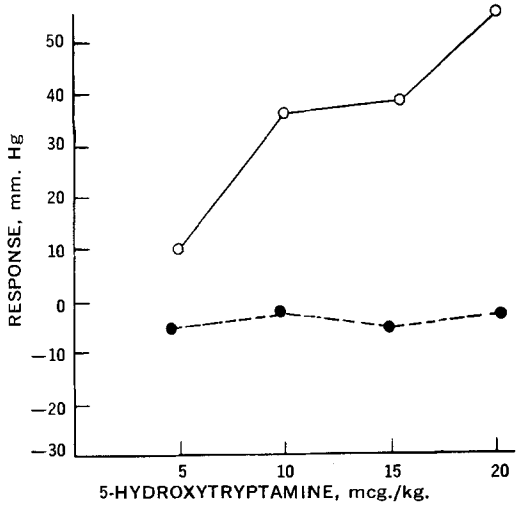

Figure 2—*Blood pressure responses to 5-hydroxytryptamine. Key: O, diastolic change, control; and ●, diastolic change after 50 mg./kg. bulbocapnine.*

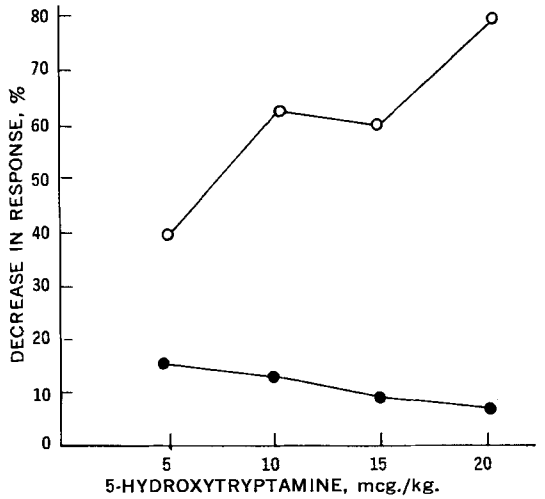

Figure 3—*Contractile force responses to 5-hydroxytryptamine. Key: O, control; and ●, after 50 mg./kg. bulbocapnine.*

cardiovascular physiology of 5-hydroxytryptamine and aid in a logical interpretation of some of its effects.

EXPERIMENTAL

Healthy mongrel dogs of either sex, weighing between 7 and 15 kg., were anesthetized with pentobarbital sodium, 30 mg./kg. i.v., and ventilated with a Harvard respirator attached through a tracheal cannula. Mean arterial blood pressure was recorded from a polyethylene catheter inserted in the carotid artery and connected to a Sanborn model 150 amplifier system or a Grass model 5 polygraph through either a Statham or Sanborn transducer. Myocardial contractile force was measured by means of a Walton-Brody strain gauge arch sutured to the right ventricle through a right thoractomy (5) and was recorded with the Sanborn or Grass instrument. Electrocardiographic recordings were made during each experiment using lead (II). The external jugular vein was cannulated for administration of drugs, all of which were washed-in with 2–5 ml. of normal saline. Serum and tissue potassium determinations were made with the Beckman 21 flame photometer.

Measurements of mean arterial blood pressure, contractile force, and EKG were made in several different series of animals, according to the schedule shown in Table I. Of the three series of experiments, the first is a determination of the responses to bulbocapnine alone;

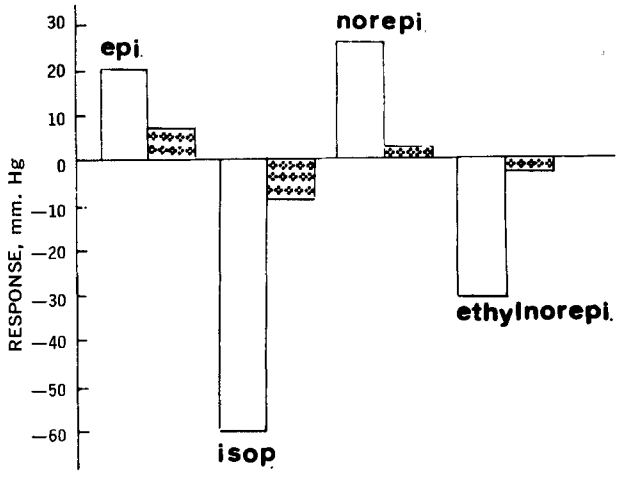

Figure 4—*Blood pressure responses to: epinephrine, 1 mcg./kg. (epi.); isoproterenol, 1 mcg./kg. (isop.); norepinephrine, 1 mcg./kg. (norepi.); and ethylnorepinephrine, 50 mcg./kg. (ethylnorepi.). Key: □, diastolic change, control; and ⊠, diastolic change after 50 mg./kg. bulbocapnine.*

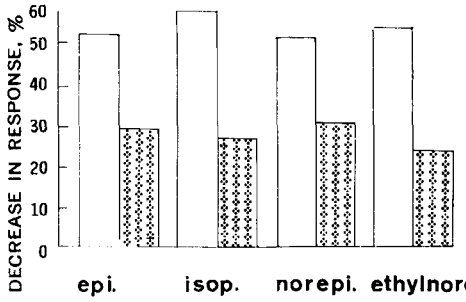

Figure 5—*Contractile force responses to: epinephrine, 1 mcg./kg. (epi.); isoproterenol, 1 mcg./kg. (isop.); norepinephrine, 1 mcg./kg. (norepi.); and ethylnorepinephrine, 50 mcg./kg. (ethylnorepi.). Key: □, control; and ⊠, contractile force after 50 mg./kg. bulbocapnine.*

the second measures the responses produced by the amines listed, given 30 min. after bulbocapnine; and the third gives the responses to the amines in the chronically bulbocapninized dog. In this last series, bulbocapnine was given to the animals for a 5-day period. On the 6th day, the animal was anesthetized with pentobarbital sodium, 30 mg./kg. i.v., and prepared surgically to record mean arterial blood pressure and myocardial contractile force. In this way it was hoped to obtain additional evidence to determine whether or not bulbocapnine was exerting its effects by releasing 5-hydroxytryptamine or catecholamine centrally, peripherally, or both.

Controls were obtained for every dose level of each drug used and consisted of an average of no less than five determinations. All responses were allowed to return to normal before subsequent injections.

All drugs were administered intravenously unless otherwise noted. The amines used in the study were dissolved in a solution of 0.1% each sodium bisulfite and chlorbutanol as preservative. Bulbocapnine was prepared just before use in each experiment. To determine the significance of the data, standard error and *t*-tests were performed (6).

RESULTS

In the first series of animals, the different levels of bulbocapnine caused no significant change in the contractile force but did produce a consistent, marked depression of diastolic blood pressure, which varied in proportion to the dosage used (Fig. 1). Electrocardiographic changes produced by the drug were seen as a prolongation of the P wave and broadening and lengthening of the QRS complex. These changes resembled those commonly seen with alterations of serum potassium levels. The level of serum potassium, determined every 10 min. during the experiment, did not show any significant change.

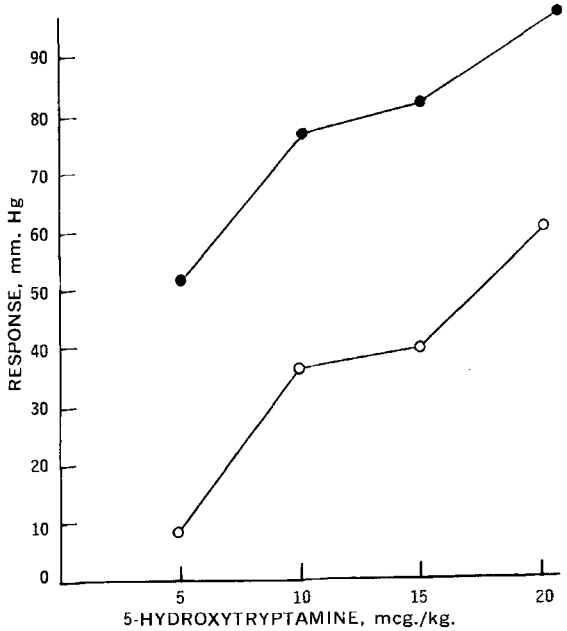

Figure 6—*Blood pressure responses to 5-hydroxytryptamine. Key: ○, diastolic change, control; and ●, diastolic change after chronic administration of bulbocapnine, 25 mg./kg. for 5 days.*

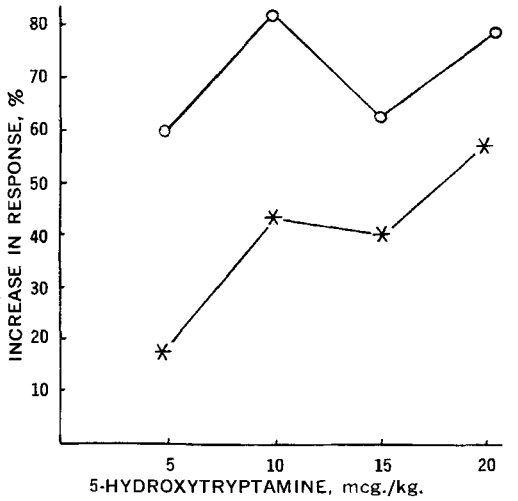

Figure 7—*Contractile force responses to 5-hydroxytryptamine. Key: *, control; and ○, contractile force after chronic administration of bulbocapnine, 25 mg./kg. for 5 days.*

The second series of experiments showed that the pressor responses produced by 5-hydroxytryptamine in the control studies were abolished by pretreatment with bulbocapnine (Figs. 2 and 3). The responses normally produced by each of the other amines were inhibited, but at no time was there evidence of a reversal of the effect of epinephrine or ethylnorepinephrine (Fig. 4). The contractile force responses of each of these agents were also reduced in every case (Fig. 5).

In the third series of experiments, the chronically bulbocapninized animals showed no physical signs or symptoms on the 6th day. The mean arterial blood pressure and contractile force responses were not different than normal. In the third series of experiment, it was found that mean arterial blood pressure and contractile force responses to 5-hydroxytryptamine given to the chronically bulbocapninized dog, on the 6th day, were greatly enhanced (Figs. 6 and 7). The action of the catecholamine, following the chronic administration of bulbocapnine, showed no significant change in

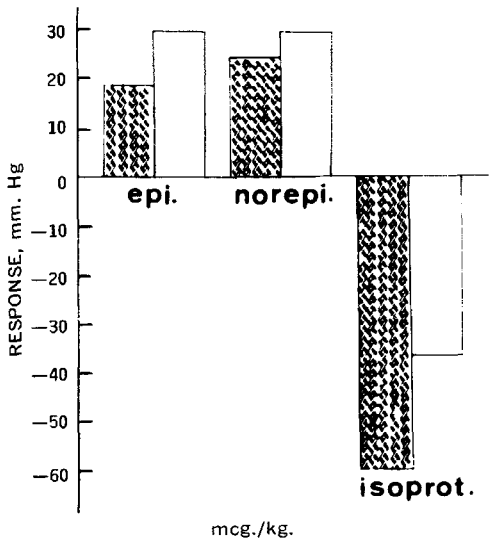

Figure 8—*Blood pressure responses to: epinephrine, 1 mcg./kg. (epi.); norepinephrine, 1 mcg./kg. (norepi.); and isoproterenol, 1 mcg./kg. (isoprot.). Key: ■, diastolic change, control; and □, diastolic change after chronic administration of bulbocapnine, 25 mg./kg. for 5 days.*

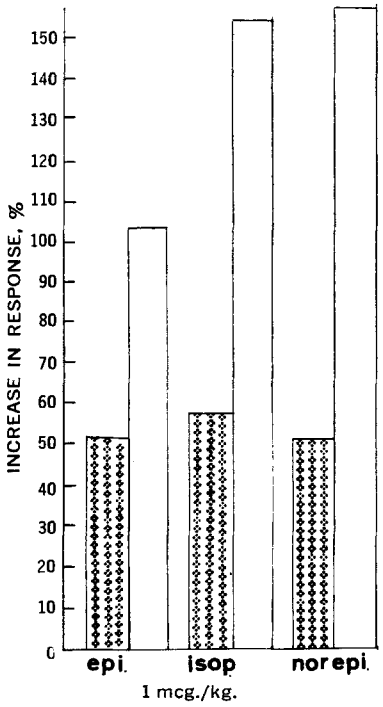

Figure 9—*Contractile force responses to: epinephrine, 1 mcg./kg. (epi.); isoproterenol, 1 mcg./kg. (isop.); and norepinephrine, 1 mcg./kg. (norepi.). Key: ▨, control; and □, contractile force after chronic administration of bulbocapnine, 25 mg./kg. for 5 days.*

regard to mean arterial blood pressure, but the contractile force effects were greatly potentiated (Figs. 8 and 9). An acute injection of 25 mg./kg. of bulbocapnine given to the chronically treated animals established a complete inhibition of the pressor response of 5-hydroxytryptamine, as well as partial inhibition of catecholamine responses, as seen in the earlier experiments.

DISCUSSION

Although the role of 5-hydroxytryptamine is still relatively unknown, evidence is accumulating to suggest that it may be a mediator in various nervous systems. The explanation of the interaction of bulbocapnine and 5-hydroxytryptamine is also equivocal. Walaszek and Chapman (2) based some of their interpretation of the action of bulbocapnine on the mediator concept and suggested that it may be an α-adrenergic blocking agent. This conclusion followed the reversal of the blood pressure response to epinephrine (7, 8). The present work failed to confirm their explanation because the reversal of epinephrine was not seen, the reduced response generally appearing to be a nonspecific depressant effect of bulbocapnine. Bulbocapnine also failed to have the characteristic blocking effect on ethylnorepinephrine (9), which one would expect of an α-adrenergic blocking agent. Consequently, the mechanism of effects of bulbocapnine on blood pressure must be explained in some other way; but the results of the present experiments and of others may indicate a rationale for its action.

It is possible that bulbocapnine may have a relatively nonspecific effect. This may be a direct action or be mediated by means of the inactivation of histaminase (4).

The present thinking relates to the peripheral storage of 5-hydroxytryptamine and its release by certain agents from storage sites (10), as well as the histaminase-inactivating action of bulbocapnine. One can postulate that bulbocapnine, by allowing an accumulation of histamine in the system, could cause an increased cellular permeability of the storage sites of 5-hydroxytryptamine as well as catecholamines. This may initiate an inhibitory action by increasing the uptake of these agents by tissue stores (11). Such uptake may more likely be selective for 5-hydroxytryptamine than for catecholamines. The blood pressure and contractile force, ordinarily stimulated by the effects of the catecholamines, are consistently inhibited but not reversed after bulbocapnine.

The responses produced by 5-hydroxytryptamine and catecholamines in chronically treated bulbocapninized animals resembled those produced by catecholamines in reserpinized animals (12, 13). Here, however, the depletion seems to be of 5-hydroxytryptamine as well as catecholamines. It is possible that bulbocapnine, acting for a prolonged period, enhances the depletion of 5-hydroxytryptamine from its receptors and then, through a sustained uptake of 5-hydroxytryptamine by tissue storage sites, makes the peripheral receptors sensitive to subsequent doses of free 5-hydroxytryptamine. Whatever the explanation, such an action by bulbocapnine has not been reported previously.

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