Z-value of low concentration polysorbate solutions in which one may expect testosterone molecules to be oriented in the hydrated polyoxyethylene surface of the micelles. The fact that the ethylene oxide chain lengths of the three polysorbates are identical and the observation that the values of testosterone solubility are nearly the same in low concentrations of all the three polysorbates support this view. The decrease in Z-value possibly results from multilayer adsorption. This proposal is substantiated by similar order of testosterone solubilization in higher polysorbate concentrations. If solubilization involved incorporation of testosterone within micellar interior, one would expect a more pronounced difference in the solubilities with a change in lipophilic moiety.

The magnitude of Z-values in 2% polysorbate solutions are comparable to those of ethanol and isopropanol, which also indicates that the environment of solubilized testosterone is quite polar. Although the hydrocarbon interior of micelles is believed to contain some water (21), its polarity might be expected to be lower than those of the alcohols.

Further studies utilizing ionic surfactants with comparable alkyl chain lengths are being conducted and will be reported in a future communication.

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Steric Aspects of Adrenergic Drugs VII

Certain Pharmacological Actions of D(−)-Pseudoephedrine

By J. B. LAPIDUS, ARTHUR TYE, and P. N. PATIL

The ability of D(−)-pseudoephedrine to influence the actions of selected adrenergic drugs was examined in both *in vivo* and *in vitro* experiments. In anesthetized dogs, pretreatment with D(−)-pseudoephedrine can reduce or block the pressor effects of the other ephedrine isomers and (+)-amphetamine. Delayed potentiation was observed with norepinephrine and epinephrine. D(−)-Pseudoephedrine did not affect the pressor effects resulting from bilateral carotid occlusion, and exhibited no unique properties on the rabbit aortic strip. D(−)-Pseudoephedrine had no intrinsic activity on the isolated rat vas deferens but could block the contractions caused by tyramine or D(−)-ephedrine, and potentiate the effects of norepinephrine. D(−)-Pseudoephedrine and D(−)-ephedrine compete for α-adrenergic sites in the reserpine pretreated rat vas deferens and can protect these receptors from dibenamine blockade. It appears that D(−)-pseudoephedrine acts at both catecholamine uptake sites and at α-receptors, but apparently lacks intrinsic effects at the latter site.

In previous papers (1, 2), the authors have presented evidence that D(−)-pseudoephedrine has a unique vascular activity when compared with other isomers of ephedrine. It has virtually no pressor activity (2), yet is a diastereoisomer of D-(−)-ephedrine, the most active pressor member of the four ephedrine isomers. Certain stereochemical consequences of this relationship led to the belief that D(−)-pseudoephedrine should, in fact, be able to antagonize the pressor response to D(−)-ephedrine (1). D(−)-Ephedrine and D(−)-pseudoephedrine have the same absolute configuration at the β-carbon atom (that bearing the hydroxyl group) (Fig. 1). If the assumption is made that the amino group, the hydroxyl group, and the phenyl ring are all involved in the drug–receptor interaction (3), then these two diastereoisomers represent a

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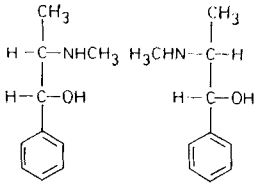

Fig. 1—Planar structures of D(-)-ephedrine (left) and D(-)-pseudoephedrine (right).

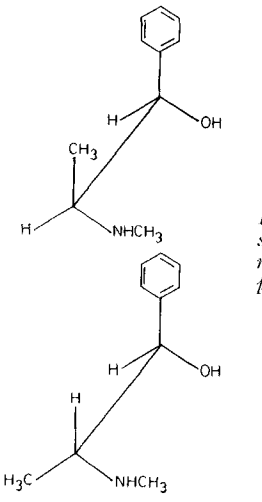

Fig. 2—Three-dimensional structures of D(-)-ephedrine (top) and D(−)-pseudoephedrine (bottom).

unique case in which the active groups in both molecules can occupy the same three points in space. This is not apparent from the Fischer projection formulas shown in Fig. 1, but becomes clear when the compounds are represented as in Fig. 2.

This structural relationship, coupled with the observed differences in pressor activity of these two compounds, led to the conjecture that D(−)-pseudoephedrine is capable of interacting with the same receptor(s) as D(−)-ephedrine, but apparently does so in a biologically unproductive manner. In other words, D(−)-pseudoephedrine may have affinity but very little or no intrinsic activity.

This paper is primarily concerned with the interactions of D(−)-pseudoephedrine with other isomers of ephedrine and related agents.

METHODS

In Vivo Experiments—Mongrel dogs of either sex, weighing 7–11 Kg., were anesthetized with sodium barbital, 330 mg./Kg. i.p. All experimental animals were pretreated with atropine sulfate, 1 mg./Kg. Blood pressure was recorded through the right carotid artery *via* a mercury manometer. In experiments involving bilateral carotid occlusion the femoral blood pressure was recorded and sodium pentobarbital,[1] 35 mg./Kg., was used as an anesthetic. The trachea was always cannulated. Respiration was recorded, when desired, on a kymograph through a tambour. Electrocardiograms were recorded on a Sanborn Twin Viso recorder.

[1] Nembutal, Abbott Laboratories, North Chicago, Ill.

In Vitro Experiments—Spirally cut aortic strips of the rabbit were prepared according to the method described by Furchgott and Bhadrakom (4). After the animal was rendered unconscious by a sharp blow on the head, a long incision was made on the skin and thoracic and abdominal contents were resected to expose the whole length of aorta. An incision was then made at the descending level of the aortic arch, and a long glass rod (about 3 mm. in diameter) passed gradually in it. The whole length of the aorta was thus removed from the rabbit. The fat and other connective tissue was carefully separated. During this procedure the aorta was kept moist throughout by means of Kreb's bicarbonate solution (5). The whole length of the aorta was cut spirally to give a strip 3–4 mm. wide. Strips 4 cm. in length were mounted in jacketed 10-ml. muscle chambers containing Kreb's bicarbonate at 37.5°. The contractions of the aortic strip were magnified by a lever in a ratio of 1:20, and counterbalanced to exert 4 Gm. of tension. The preparations were oxygenated by 95% O_2 and 5% CO_2 and allowed to stabilize for at least 2 hr. before any drug induced contractions were recorded *via* a frontal point lever on a slowly moving smoked kymograph. The cumulative dose-response curves were obtained as described by Van Rossum (6). No attempt was made to make two dose-response curves from the same strip. It required 10 to 15 min. to reach a plateau after addition of each dose of drug. In antagonism studies, the preparation was exposed to the antagonist for 10 min. and the dose-response curve of the agonist then obtained in presence of the antagonist.

Rats weighing 100–150 Gm. were killed by a sharp blow on the head. A vas deferens was isolated from all connective tissues and suspended in a jacketed 10-ml. muscle chamber which contained Tyrode's solution at 37–37.5°. The composition of the Tyrode's solution was as follows: NaCl, 137 m*M*; KCl, 2.68 m*M*; $CaCl_2(2H_2O)$, 1.76 m*M*; $MgCl_2(6H_2O)$, 0.88 m*M*; NaH_2PO_4, 0.36 m*M*; $NaHCO_3$, 12 m*M*; glucose, 5.5 m*M*; demineralized water was used to make the solution. A mixture of oxygen (95%) and CO_2 (5%) was bubbled through the solution. Drug-induced contractions were recorded on a smoked drum *via* a light lever (magnification: 20, tension approximately 350 mg.) which was always under the influence of low vibrations produced by a small electric motor.

Receptor protection experiments as introduced by Furchgott (7) were carried out on isolated rat vas deferens. Dibenamine (10^{-6} *M*) was selected as an irreversible α-adrenergic blocker. These experiments were carried out in the reserpine-pretreated (5 mg./Kg. i.p. 8 to 16 hr. previously) rats, because D(−)-ephedrine is classified as a mixed acting amine on isolated rat vas deferens (8). Therefore, norepinephrine liberated from the nerve endings would complicate the protection of α-adrenergic receptors by D(−)-ephedrine.

DRUGS

The optical isomers of ephedrine were prepared by the method described by LaPidus *et al.* (1). For each experiment fresh solutions of the isomers were made in physiological saline by the addition of a small amount of dilute hydrochloric acid. The following drugs were obtained from commercial

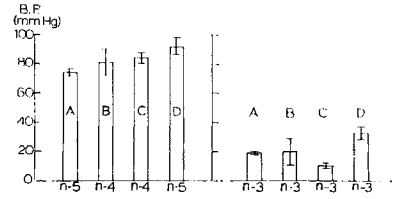

Fig. 3—Reduction of pressor effects of D(-)-ephedrine L(+)-ephedrine, D(+)-amphetamine, and L(+)-pseudoephedrine by 30-min. pretreatment with D(-)-pseudoephedrine in anesthetized dog. Key: A, *D(-)-ephedrine, 0.33 mg./Kg.;* B, *L(+)-ephedrine, 0.99 mg./Kg.;* C, *L(+)-pseudoephedrine, 1.65 mg./Kg.;* D, *D(+)-amphetamine, 0.36 mg./Kg.; vertical lines indicate standard errors of mean [control data from Patil* et al. *(2)];* n, *number of dogs;* B.P., *blood pressure rise in mm. of Hg over preinjection level; left, control; right, D(-)-pseudoephedrine.*

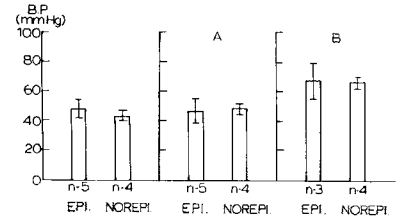

Fig. 4—Effect of D(-)-pseudoephedrine (3.3 mg./Kg.) on the pressor responses to epinephrine (EPI), *1.5 mg./Kg. and norepinephrine* (NOREPI) *0.4 mcg./Kg. in anesthetized dogs. Key:* B.P., *blood pressure rise in mm. of Hg over preinjection level;* n, *number of observations;* A, *epinephrine and norepinephrine given 10 to 20 min. after D(-)-pseudoephedrine;* B, *epinephrine and norepinephrine given 45 to 60 min. after D(-)-pseudoephedrine; vertical lines indicate standard errors of the mean; right, control; middle and left, D(-)-pseudoephedrine.*

sources: D(+)-amphetamine sulfate, norepinephrine bitartrate,[2] reserpine phosphate,[3] epinephrine bitartrate,[4] tyramine HCl, and dibenamine HCl. All the weights given refer to free base except for amphetamine which refers to its sulfate. The terminology used for ephedrine isomers has been described previously (2).

Whenever possible the standard errors of the mean were calculated; significance between two means was tested by *t* test. Otherwise, for qualitative purposes, at least 3 observations were made in different animals. Since most of these drugs may affect the responses of one another, each observation was made in an individual animal.

RESULTS

The Effects of Pretreatment with D(−)-Pseudoephedrine—In preliminary experiments eight dogs were pretreated with D(−)-pseudoephedrine (0.33, 3.3, 9.9, 16.5 mg./Kg.) 30 min. before a challenging dose of D-(−)-ephedrine was given. [The blocking ability of D(−)-pseudoephedrine was found to be maximal when the pretreatment interval was

[2] Levophed, Winthrop Laboratories, New York, N. Y.
[3] Serpasil, Ciba Pharmaceutical Co., Summit, N. J.
[4] Suprarenin, Winthrop Laboratories, New York, N. Y.

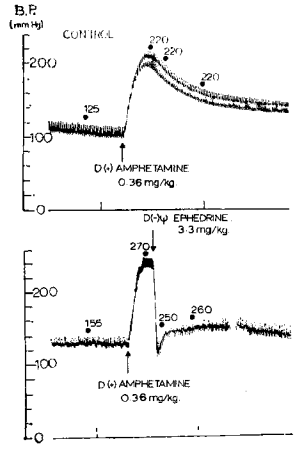

Fig. 5—Antagonistic effect of D(-)-pseudoephedrine on the pressor effects of D(+)-amphetamine in anesthetized dogs. Key: B.P., *blood pressure in mm. of Hg; heat rate (beats/min.) indicated by numbers above the blood pressure tracing; time mark, 10 min.*

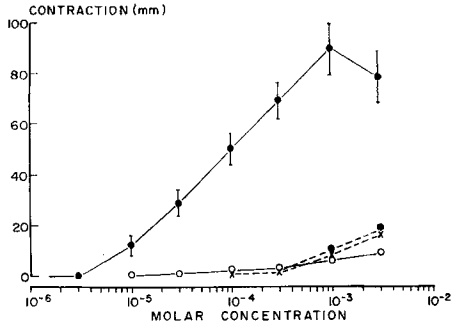

Fig. 6—Effect of ephedrine isomers on the contraction of the rabbit aortic strip. D(-)-ephedrine (●–●), L(+)-ephedrine (○—○), L(+)-pseudoephedrine (×----×), D(-)-pseudoephedrine (●···●). Nine to 12 strips used for each isomer. Vertical lines indicate standard errors of the mean. In the case of L(+)-ephedrine, L(+)-pseudoephedrine, and D(-)-pseudoephedrine, standard errors markedly overlapped each other.

reasonably short.] Doses of 9.9 or 16.5 mg./Kg. completely blocked the blood pressure, heart rate, and respiratory effect of D(−)-ephedrine (0.33 mg./Kg.). D(−)-Pseudoephedrine itself shows temporary depressor effects in anesthetized animals (2). Animals pretreated with 3.3 mg./Kg. of D-(−)-pseudoephedrine 30 min. before challenging with one of the following amines: D(−)-ephedrine, 0.33 mg./Kg.; L(+)-ephedrine, 0.99 mg./Kg.; L(+)-pseudoephedrine, 1.65 mg./Kg.; or D(+)-amphetamine sulfate, 0.36 mg./Kg., exhibited marked reduction of the pressor effects of these amines (Fig. 3).

At the 0.33-mg./Kg. dose level D(−)-pseudoephedrine did not significantly modify the pressor effects of epinephrine or norepinephrine. However, when the dose of D(−)-pseudoephedrine was increased to 3.3 mg./Kg., a potentiation of pressor effects was noted. This potentiation was more

TABLE I—CONTRACTION OF RABBIT AORTIC STRIPS TO 10^{-3} *M* D(−)-EPHEDRINE AFTER DOSE RESPONSE CURVES OF OTHER ISOMERS OF EPHEDRINE ARE COMPLETED

	Mean Contraction, mm. (± S.E.M.)			
	Control	After L(+)-Ephedrine	After L(+)-Pseudoephedrine	After D(−)-Pseudoephedrine
D(−)-Ephedrine (10^{-3} *M*)	89, ± 11	14, ± 5	48, ± 15	28, ± 9
No. of observations	10	9	6	9
P value compared with control		<0.001	<0.05	<0.01

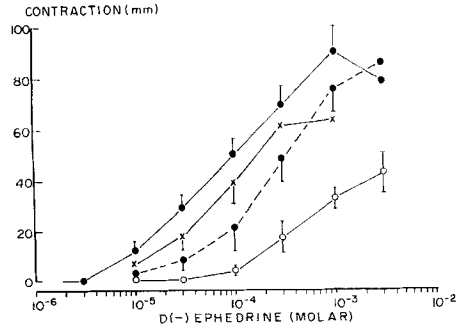

Fig. 7—Dose-response curves of D(-)-ephedrine in the presence of L(+)-ephedrine (10^{-3} M) (O—O), L(+)-pseudoephedrine (×—×) (10^{-3} M), and D(-) pseudoephedrine (10^{-3} M) (●---●). Vertical lines indicate standard errors of the mean. Average of 6, strips for each isomer.

marked 45 to 60 min. after administration (Fig. 4). The pressor effects of epinephrine (in terms of both duration and magnitude) tended to be reduced if it was given 10 to 20 min. after a dose of 9.9 mg./Kg. of D(−)-pseudoephedrine. In four experiments the average control rise in blood pressure to 0.75 mcg./Kg. of epinephrine was 29 mm. of Hg (S.E. ± 4) and that after D(−)-pseudoephedrine was 18 mm. of Hg (S.E. ± 7). Under similar conditions, the pressor effects of norepinephrine, 0.4 mcg./Kg., were not affected. In four experiments the average control rise in blood pressure was 44 mm. of Hg (S.E. ± 7), and that after D(−)-pseudoephedrine was 44 mm. of Hg (S.E. ± 18). While the intensity of the response to norepinephrine remained the same, the duration was increased.

D(−)-Pseudoephedrine was tested for its ability to modify bilateral carotid occlusion pressor effects. In doses of 3.3 or 9.9 mg./Kg. (two animals for each dose), it did not affect the carotid occlusion pressor effects up to 30 to 60 min. after injection.

When D(−)-pseudoephedrine, 3.3 mg./Kg., was given at the height of pressor responses to D(−)-ephedrine, 0.33 mg./Kg. (3 experiments), an immediate reduction in pressor response occurred in all experiments (Fig. 5). In control experiments the pressor effects of D(−)-ephedrine and D(+)-amphetamine sulfate persisted for 15 to 20 min. The increase in heart rate was not effectively antagonized.

Rabbit Aortic Strip—D(−)-Ephedrine is the only isomer which showed a marked contraction of the aortic strips. Other isomers—namely, L(+)-ephedrine, L(+)-pseudoephedrine, and D(−)-pseudoephedrine did not show any appreciable effects. The maximal effects produced by less active isomers were less than 20% of the effect produced by D(−)-ephedrine. The negative log ED_{50} of D(−)-ephedrine is 4.19 (S.E. ± 0.08) which is obtained by plotting every single dose-response curve and from log transformed values. The results are illustrated in Fig. 6.

If $10^{-3}M$ concentration of D(−)-ephedrine was added in the tissue bath after complete dose-response curves of lesser active isomers were constructed, there was a marked reduction of the maximal effects of ephedrine (Table I).

In the other series of experiments, the dose-response curves of D(−)-ephedrine were constructed in the presence of 10^{-4} *M* and 10^{-3} *M* concentrations of less active isomers. In the lower concentrations there was not any significant shift of the dose-response curve of D(−)-ephedrine. In higher concentrations, however, there was a significant shift to the right. L(+)-Ephedrine appeared to be the most effective in antagonizing the action of D(−)-ephedrine. The height of the dose-response curve of D(−)-ephedrine in the presence of 10^{-3} *M* L(+)-ephedrine was depressed (Fig. 7 and Table II).

Rat Vas Deferens—Tyramine, 10^{-4} *M*, and D(−)-ephedrine, 10^{-4} *M*, produce a maximum or near maximum contraction of rat vas deferens (9). D(−)-Pseudoephedrine, in concentrations of 10^{-4} *M* and 10^{-3} *M*, markedly antagonized the effects of tyramine and D(−)-ephedrine. D(−)-Pseudoephedrine did not show any intrinsic effects (Tables III and IV). The same concentrations of D(−)-pseudoephedrine produced a clear cut potentiation of norepinephrine (Fig. 8).

In receptor protection experiments, both D(−)-

TABLE II—NEGATIVE LOG ED_{50} VALUES OF D(−)-EPHEDRINE IN THE PRESENCE OF 10^{-3} *M* CONCENTRATION OF L(+)-EPHEDRINE, L(+)-PSEUDOEPHEDRINE, AND D(−)-PSEUDOEPHEDRINE ON THE RABBIT AORTIC STRIP

	Concn. of Antagonist, 10^{-3} *M*			
	Control	L(+)-Ephedrine	L(+)-Pseudoephedrine	D(−)-Pseudoephedrine
D(−)-Ephedrine ED_{50}	4.19 (S.E. ± 0.08)	3.36 (S.E. ± 0.11)	4.01 (S.E. ± 0.07)	3.65 (S.E. ± 0.11)
No. of observations	10	6	6	6
P value compared with control		<0.001	<0.05	<0.01

TABLE III—REDUCTION OF TYRAMINE INDUCED CONTRACTIONS OF RAT VAS DEFERENS IN THE PRESENCE OF VARIOUS CONCENTRATIONS OF D(−)-PSEUDOEPHEDRINE

	Tyramine (10^{-4} *M*) Mean Contraction, mm. (± S.E.M.)					
	Control[a]	After 10^{-5} *M* D(−)-Pseudoephedrine[b]	Control[a]	After 10^{-4} *M* D(−)-Pseudoephedrine[b]	Control[a]	After 10^{-3} *M* D(−)-Pseudoephedrine[b]
	152, ± 10	121, ± 5	133, ± 8	85, ± 4	137, ± 12	25, ± 10
n[c]	9	9	8	8	6	6
P value	<0.01		<0.001		<0.001	

[a] Controls were obtained on the contralateral side of the same rat. [b] Added 3 min. prior to tyramine. [c] *n*, number of observations.

TABLE IV—REDUCTION OF D(−)-EPHEDRINE INDUCED CONTRACTIONS OF RAT VAS DEFERENS IN THE PRESENCE OF VARIOUS CONCENTRATIONS OF D(−)-PSEUDOEPHEDRINE

	D(−)-Ephedrine (10^{-4} *M*) Mean Contraction, mm. (±S.E.M.)					
	Control[a]	After 10^{-5} *M* D(−)-Pseudoephedrine[b]	Control[a]	After 10^{-4} *M* D(−)-Pseudoephedrine[b]	Control[a]	After 10^{-3} *M* D(−)-Pseudoephedrine[b]
	56, ± 7	47, ± 5	36, ± 6	8, ± 3	50, ± 8	2, ± 2
n[c]	6	6	8	8	8	8
P value	>0.05		<0.001		<0.001	

[a] Controls were obtained on the contralateral sides of the same rat. [b] Added 3 min. prior to D(−)-ephedrine. [c] *n*, number of observations.

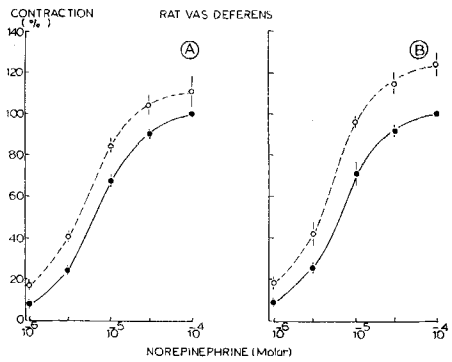

Fig. 8—Key: A, *potentiation of norepinephrine in the presence of* 10^{-4} M *D(-)-pseudoephedrine;* B, *potentiation of norepinephrine in the presence of* 10^{-3} M *D(-)-pseudoephedrine. Each point of the curve represents an average of eight observations. Vertical lines indicate standard errors of the mean. Vas deferens was exposed to D(-)-pseudoephedrine for 3 min. before a dose-response curve of norepinephrine was repeated.*

pseudoephedrine (10^{-3} *M*) and D(−)-ephedrine (10^{-3} *M*) completely protected the α-adrenergic receptors from dibenamine blockade in the reserpine pretreated tissues. Results are summarized in Table V.

D(−)-Ephedrine produced an average 41 mm. (S.E. ± 7.8) contraction of the reserpine pretreated vas deferens. Under similar conditions, lower concentrations, 3×10^{-4} *M*, of D(−)-pseudoephedrine and D(−)-ephedrine also protected the α-adrenergic receptors to the extent of 26% (S.E. ± 11) and 44% (S.E. ± 6.9), respectively.

DISCUSSION

D(−)-Ephedrine and D(−)-pseudoephedrine are each capable of attachment to three identical points on a receptor (Fig. 2). Since the pressor effects of D(−)-pseudoephedrine are markedly inferior to those of D(−)-ephedrine (2), it was anticipated that it might antagonize the actions of the latter compound. The authors found that both *in vivo* and *in vitro* D(−)-pseudoephedrine does indeed markedly reduce the effects of D(−)-ephedrine and other "indirectly" acting sympathomimetic amines such as amphetamine and tyramine. It is interesting to note that D(−)-pseudoephedrine does not have any "intrinsic" effects on isolated rat vas deferens and at concentrations in which it antagonizes tyramine and ephedrine, potentiates the effects of norepinephrine. This led to the conclusion that D(−)-pseudoephedrine possibly acts at the catecholamine uptake sites. In other words, it has "cocaine-like" effects at the sympathetic nerve endings.

TABLE V—PROTECTION OF α-ADRENERGIC RECEPTORS BY D(−)-PSEUDOEPHEDRINE AND D(−)-EPHEDRINE IN RESERPINE PRETREATED (5 mg./Kg., 8–16 hr.) RAT VAS DEFERENS

Norepinephrine (10^{-4} *M*) Mean Contraction, mm. (± S.E.M.)					
Control[a]	Tissue Incubated with Dibenamine,[b] 10^{-6} *M*	Control[a]	Tissue Incubated with D(−)-Pseudoephedrine[c] (10^{-3}*M*) and Dibenamine,[b] 10^{-6} *M*	Control[a]	Tissue Incubated with D(−)-Ephedrine[c] (10^{-3}*M*) and Dibenamine,[b] 10^{-6} *M*
141, ± 5	0	148, ± 3	140, ± 6	150, ± 1	151, ± 4
n^d = 8		*n* = 5		*n* = 5	

[a] Controls were obtained from the contralateral side on the same rat. [b] Incubation time was 10 min., then tissue washed 4 times and 10 min. after the last wash norepinephrine was added. [c] Five minutes prior to dibenamine, D(−)-pseudoephedrine and D(−)-ephedrine were added in the tissue bath. [d] *n*, number of observations.

By using receptor protection experiments, it was possible to demonstrate that D(−)-pseudoephedrine also competes for the α-adrenergic sites. However, this effect must be very weak because the effects of exogenous norepinephrine are potentiated (*i.e.*, the competition of D(−)-pseudoephedrine at α-receptors is overcome by norepinephrine, the uptake of which is being prevented in the nerve endings). Thus, D(−)-pseudoephedrine is capable of acting at the catecholamine uptake sites and the α-adrenergic sites; however, it lacks intrinsic activity at the latter site.

The pharmacological effects of L(+)-pseudoephedrine and L(+)-ephedrine are similar on the aortic strips which support the previous report that there is a small difference between the pressor effects of these L-diastereoisomers in the dog (2).

D(−)-Ephedrine is the only isomer of ephedrine which produces a marked contraction of rabbit aortic strips. In the presence of 10^{-3} *M* concentrations of L(+)-ephedrine, L(+)-pseudoephedrine, or D(−)-pseudoephedrine, the dose-response curves of D(−)-ephedrine are shifted to the right.

On the isolated rat vas deferens D(−)-pseudoephedrine did not show any intrinsic effects. However, the contractions due to tyramine and D(−)-ephedrine were markedly antagonized by 10^{-4} *M* and 10^{-3} *M* D(−)-pseudoephedrine, while the effects of norepinephrine were potentiated. In addition, D(−)-pseudoephedrine and D(−)-ephedrine also compete for the α-adrenergic sites in the reserpine pretreated animals. D(−)-Pseudoephedrine appears to act at both the catecholamine uptake site and the α-adrenergic site, but apparently lacks intrinsic effects at the latter site.

SUMMARY

In anesthetized dogs, pretreatment (30 min.) with D(−)-pseudoephedrine, 3.3 mg./Kg., can reduce or block the pressor effects of D(−)-ephedrine, L(+)-ephedrine, L(+)-pseudoephedrine, and D(+)-amphetamine. D(−)-Pseudoephedrine also promptly reduces the pressor effects, if given during the height of response. The pressor effects of norepinephrine and epinephrine appeared to be potentiated by D(−)-pseudoephedrine. Such a potentiation was best seen 45 to 60 min. after the administration of the isomer. The pressor effects due to bilateral carotid occlusion were unaffected by D(−)-pseudoephedrine.

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Differentiating Nonaqueous Titration of Salicylic Acid and Acetylsalicylic Acid Combination

By SONG-LING LIN

Synthetic mixtures of salicylic acid and acetylsalicylic acid are differentiated by potentiometric nonaqueous titration. With sodium methoxide or tetrabutylammonium hydroxide titrant and glass-calomel electrode system, dimethylformamide is found to be the best differentiating solvent. The effect of the solvent in titration and differentiation of salicylic acid and acetylsalicylic acid in water and dimethylformamide is illustrated and interpreted. Various solvent–titrant–electrode combinations are employed to explore their effects on the sensitivity of the differentiating titration. The presence of water in the titration solvent is demonstrated to be highly detrimental and undesirable on differentiation. The proposed procedure is simple, accurate, and applicable even when there is a disproportionate concentration of the components. The work suggests that by a proper combination of solvent, titrant, and electrode system, it should be possible to differentiate potentiometrically both components of acidic or basic mixtures whose dissociation constants are well below the theoretical limit of 16.

A VARIETY OF procedures (1–8) have been proposed for the analysis of acetylsalicylic acid and one of its degradation products, salicylic acid. These methods involve colorimetry, chromatography, and spectrophotometry. However, a search of the literature for titrimetric techniques applicable to differentiating salicylic acid–acetylsalicylic acid combination was not successful. It was the purpose of this study to develop such a procedure.

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