THE JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS

Vol. 184, No. 2
Printed in U.S.A

VASOCONSTRICTION PRODUCED BY HALLUCINOGENS ON ISOLATED HUMAN AND SHEEP UMBILICAL VASCULATURE[1]

D. C. DYER AND D. W. GANT[2,3]

Department of Pharmacology and The Anesthesia Research Center, School of Medicine, University of Washington, Seattle, Washington

Accepted for publication October 10, 1972

ABSTRACT

DYER, D. C. AND D. W. GANT: Vasoconstriction produced by hallucinogens on isolated human and sheep umbilical vasculature. J. Pharmacol. Exp. Ther. **184**: 366–375, 1973.

The effects of halluncinogenic drugs on helically cut strips of human umbilical veins and sheep umbilical arteries were studied. Muscle activity at 37°C was recorded isotonically under 1 g of tension. Bufotenine, psilocin, psilocybin, mescaline and *d*-lysergic acid diethylamide (LSD) all produced contractions of umbilical vasculature with LSD being the most potent. The contractions to all hallucinogens were antagonized by cinanserin. In addition, 2-bromolysergic acid diethylamide anatagonized responses to mescaline and LSD on sheep umbilical arteries. Concentrations of piperoxan, tripelennamine and atropine which antagonized responses to epinephrine, histamine and acetylcholine, respectively, did not antagonize responses to LSD, bufotenine or serotonin. We conclude that all of the hallucinogens studied produced contractions *via* serotonergic receptors on umbilical vasculature.

A number of drugs have been observed to constrict umbilical blood vessels. Among those reported to be potent agonists on human umbilical vasculature are: bradykinin (Gokhale *et al.*, 1966; Klinge *et al.*, 1966; Eltherington *et al.*, 1968) serotonin (5-hydroxytryptamine) (Somlyo *et al.*, 1965; Aström and Samelius, 1957; Klinge *et al.*, 1966) and *d*-lysergic acid diethylamide (LSD) (Gant and Dyer, 1971). Although the umbilical vasculature for sheep and man serves a similar function, that from sheep responds somewhat differently to certain agonists. For instance: bradykinin constricts human umbilical vessels (Eltherington *et al.*, 1968) but not those from sheep (Dyer, 1970a); angiotensin is a potent constrictor of sheep (Dyer, 1970a) but not human (Somylo *et al.*, 1965; Gokhale *et al.*, 1966) umbilical arteries and veins; cocaine potentiates responses to serotonin on sheep (Dyer, 1970b) but not human umbilical vasculature (unpublished observations); histamine constricts human umbilical arteries and veins and sheep umbilical veins but not sheep umbilical arteries (Dyer *et*

Received for publication November 8, 1971.
[1] This investigation was supported in part by U.S. Public Health Service, National Institutes of Health Grant GM 15991 and by U.S. Public Health Service Training Grant GM 01458.
[2] A portion of the data presented in this manuscript was taken from a thesis presented to the Department of Pharmacology, The Graduate School, The University of Washington, in partial fulfillment of the requirements for the degree of Master of Science.
[3] Presently enrolled in the Medical School, University of Washington.

Send reprint requests to: Donald C. Dyer, Department of Pharmacology SJ-30, School of Medicine, University of Washington, Seattle, Wash. 98195.

al., 1972). Also, *beta* adrenergic receptors are present in sheep (Dyer, 1970a) but not human umbilical vasculature (Somylo *et al.*, 1965; Eltherington *et al.*, 1968). Because our laboratory is interested in the umbilical vasculature as a possible site of drug action in the fetal circulation as well as in finding an animal model of the umbilical vasculature which closely mimics that of man, we feel it is very important to ascertain if responses to drugs are species specific. With this consideration in mind, we have enlarged upon our initial investigation in which LSD was found to be an effective agonist on human umbilical vein strips (Gant and Dyer, 1971) to include other hallucinogens and for comparative purposes extended these studies to isolated sheep umbilical vasculature whenever possible. A preliminary report of these findings has been communicated (Dyer and Gant, 1971).

Methods

Human umbilical cords were obtained from University Hospital (Seattle, Wash.) within 15 minutes of normal delivery. The tissues were placed in Krebs-Henseleit solution modified to contain 10 μg/ml of disodium ethylenediamine tetraacetic acid. Sheep umbilical cords were obtained as previously described (Dyer, 1970a). Both sheep umbilical arteries and human umbilical veins were helically cut. Strips of vascular smooth muscle approximately 2 cm long were placed in a series of 10-ml isolated organ baths of the drain-out type. The tissues were placed under 1 g of tension and allowed to equilibrate for about two hours before starting the experiment. The baths were maintained at 37°C and oxygenated by bubbling a mixture of oxygen–carbon dioxide (95:5) through the bottom of the bath. The contractions were magnified ×10 and recorded isotonically on a kymograph drum.

The following drugs were used in this study: angiotensin amide, serotonin creatinine sulfate, acetylcholine chloride, *l*-epinephrine hydrochloride, bradykinin, *d*-lysergic acid diethylamide tartrate, mescaline hydrochloride, psilocin, psilocybin, bufotenine bioxalate monohydrate, cinanserin hydrochloride, 2-bromolysergic acid diethylamide (BOL), piperoxan hydrochloride, atropine sulfate, and tripelennamine hydrochloride.

Results

Human umbilical vein preparations. Serotonin was routinely used to establish the maximum tissue contraction of both human umbilical veins and sheep umbilical arteries. Serotonin was a very effective agonist and contractions produced to it were reproducible during the time course of the experiments (fig. 1). Cinanserin antagonized responses to serotonin and shifted the dose-response curve to the right. Other serotonin antagonists such as BOL and methysergide were used initially but they contracted the vein strips. Because of their intrinsic activity, they were not useful as antagonists to serotonin on human umbilical veins.

Psilocin and psilocybin contracted human umbilical vein strips. Both agonists were clearly less potent than serotonin and were antagonized by cinanserin (fig. 2). Bufotenine and mescaline

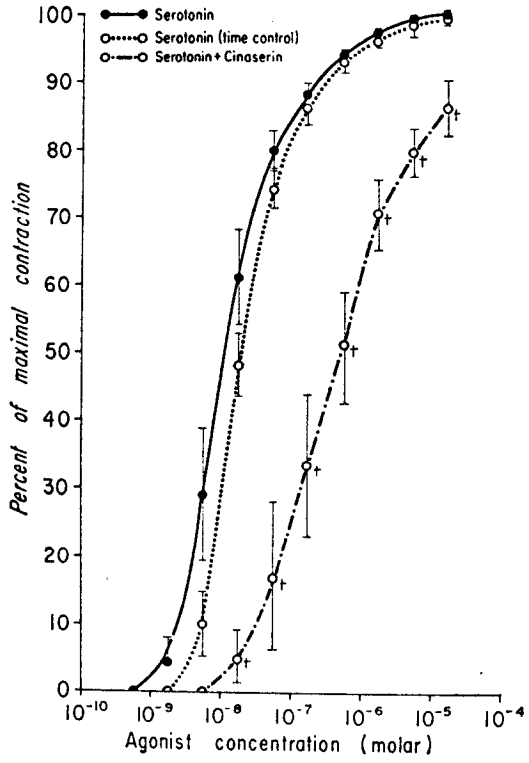

FIG. 1. Cumulative dose-responses to serotonin were obtained on isolated strips of human umbilical veins. Cinanserin hydrochloride (3×10^{-7} M) was incubated with the tissue for 10 minutes prior to exposure to serotonin. Note the small shift of the dose-response curve to the right with time which was not significantly different from control and the much greater shift in the presence of cinanserin. Vertical bars represent ± S.E.M. of five to seven experiments and †'s represent points on the cinanserin-serotonin curve which are significantly different from the serotonin control ($P < .05$).

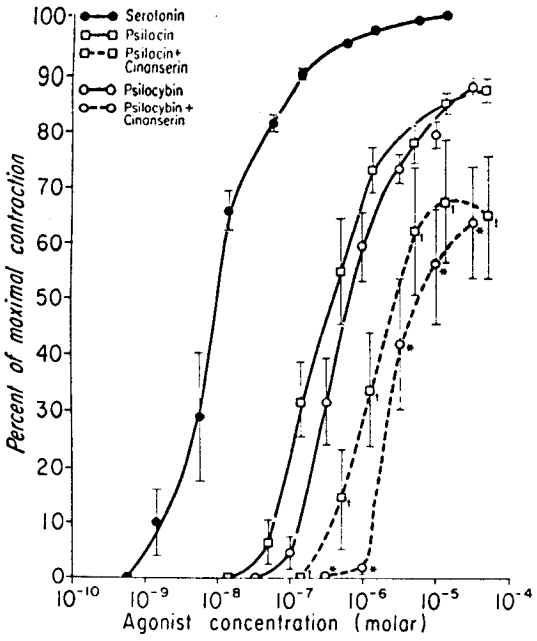

FIG. 2. A comparison of the vasoconstrictor activity of serotonin, psilocin and psilocybin on isolated strips of human umbilical veins. Cinanserin hydrochloride (3×10^{-7} M) was incubated with the tissue for 10 minutes before exposing the tissue to either psilocin or psilocybin. Cinanserin antagonized responses to both psilocin and psilocybin. Vertical bars represent ± S.E.M. of six experiments. †'s and *'s represent points on the curves which are significantly different from their respective controls of psilocin and psilocybin ($P < .05$).

also contracted umbilical vein strips and responses to each were antagonized by cinanserin (fig. 3). In order to ascertain if the antagonism by cinanserin could be attributed to a nonspecific depression of the smooth muscle, we used bradykinin as an agonist. Near maximal responses to bradykinin were blocked by cinanserin (fig. 4), but the ED50 for bradykinin was not significantly altered (table 1).

From the previous figures and table, it is clear that cinanserin antagonized responses to serotonin, psilocin, psilocybin, bufotenine and mescaline to a greater degree than those to bradykinin. We also investigated the effect of tripelennamine on responses to serotonin, histamine and the hallucinogens to rule out the possibility of a histaminergic receptor involvement. It can be seen from table 1 that tripelennamine only antagonized responses to histamine. We did not investigate the effects of atropine or piperoxan on responses to the hallucinogens since reliable responses to either acetylcholine or epinephrine could not be obtained.

Sheep umbilical artery preparations. Bufotenine produced contractions of isolated sheep umbilical arteries which were antagonized by cinanserin (fig. 5). Bufotenine and serotonin were essentially equiactive in the lower concentration range but bufotenine did not produce a maximal tissue contraction. Responses to bufotenine were blocked by cinanserin but not by piperoxan or atropine (table 2). Psilocin and psilocybin also elicited contractions, but the threshold concentration to contract the tissue was approximately 10-fold greater than that of serotonin whereas the maximal response was only 40% of that to serotonin ($N = 4$). In two experiments, the contractions to both psilocin and psilocybin were antagonized by cinanserin.

For reference use in future experiments, complete dose-response curves to acetylcholine and epinephrine were obtained (fig. 6). It is clear that acetylcholine and epinephrine are not as

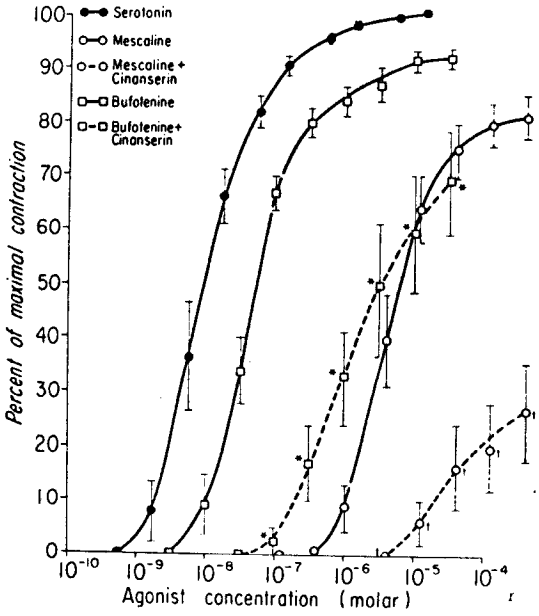

FIG. 3. Experiments comparing the activity of serotonin, mescaline and bufotenine on isolated strips of human umbilical veins. Both mescaline and bufotenine induced contractions were antagonized by cinanserin hydrochloride (3×10^{-7} M). The tissues were incubated with the cinanserin for 10 minutes before exposure to mescaline or bufotenine. The vertical bars represent ± S.E.M. of five to six experiments. †'s and *'s represent points on the curves which are significantly different from their respective controls of mescaline and bufotenine ($P < .05$).

potent as serotonin and responses to each were blocked by atropine and piperoxan, respectively. Atropine and piperoxan in these concentrations do not antagonize responses to serotonin (Dyer, 1970a).

Mescaline evoked contractions but required a higher concentration than serotonin. To investigate the receptors mediating the contraction to mescaline, we chose to employ several antagonists, *i.e.*, piperoxan, BOL and cinanserin. Piperoxan (3.7×10^{-7} M), in a concentration which greatly antagonized responses to epinephrine (fig. 6), did not significantly alter contractions to mescaline or serotonin. Therefore, a 10-fold higher concentration (3.7×10^{-6} M) was employed. This concentration of piperoxan significantly antagonized responses to both mescaline and serotonin (table 2; fig. 7). Contractions to mescaline were significantly blocked by BOL and cinanserin (fig. 7) to such an extent that the 50% maximal tissue response was not obtained in their presence. Hence, the change in the ED50 in the presence of these antagonists, as tabulated in table 2, could not be obtained.

In order to ascertain whether the inhibition by cinanserin could be ascribed to a nonspecific depression, we chose angiotensin as the test agonist. It is readily apparent from figure 8 that cinanserin did not inhibit contractions to angiotensin whereas it greatly antagonized responses to serotonin.

LSD. LSD contracted isolated human umbilical veins and sheep umbilical arteries. It is not possible to obtain cumulative dose responses to LSD on these tissues (Gant and Dyer, 1971). Therefore, to investigate the receptors involved in the LSD-induced contraction, complete dose responses were obtained to serotonin on paired tissues. After washout of the bath and return of the tissues to base line, the tissues then were treated as follows: one tissue was incubated with an antagonist (atropine, piperoxan, cinanserin or BOL) for 10 minutes; then, without removing the antagonist, LSD was added to both tissues simultaneously and the response was recorded. An example of such an experiment using sheep umbilical arteries is represented in figure 9. It is clear that cinanserin antagonizes responses to LSD. In parallel experiments, BOL blocked responses to LSD but piperoxan and atropine in concentrations 10-fold greater than those needed to antagonize epinephrine and acetylcholine, respectively, did not (table 3). On isolated human umbilical veins, cinanserin antagonized responses to LSD in a manner comparable to that observed on sheep umbilical arteries ($N = 5$).

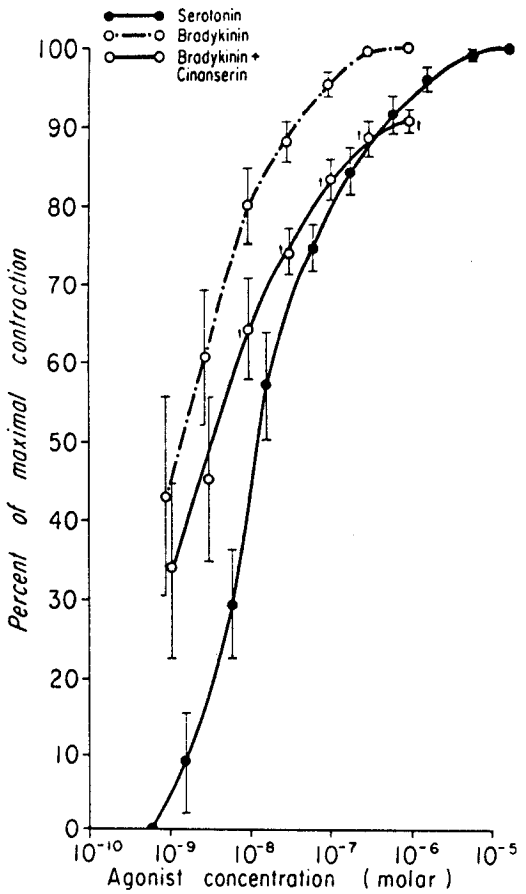

FIG. 4. A comparison of the vasoconstrictor activity of serotonin and bradykinin on isolated strips of human umbilical veins. Exposure to cinanserin hydrochloride (3×10^{-7} M) for 10 minutes did antagonize responses to bradykinin somewhat but not nearly as much as responses to serotonin were antagonized (see fig. 1). Vertical bars represent ± S.E.M. of four to five experiments. †'s represent points on the cinanserin treatment curve which are significantly different from bradykinin alone ($P < .05$).

Discussion

Cumulative dose responses to psilocin, psilocybin, mescaline, bufotenine and serotonin were obtained on both isolated sheep umbilical arteries and human umbilical veins. All of these amines were inhibited by cinanserin, a serotonin antagonist (Rubin *et al.*, 1964). Cinanserin did not

TABLE 1

Human umbilical vein: A comparison of the concentration of various agonists required to produce a contraction equal to that obtained at the ED50 of serotonin

	N[a]	ED50 ± S.E.M.	Dose-Ratio at ED50; Treated/Control
		M	
A. Serotonin (control)	7	$1.2 \times 10^{-8} \pm 4.3 \times 10^{-9}$	
Serotonin + cinanserin (3×10^{-7} M)	6	$4.2 \times 10^{-7} \pm 1.3 \times 10^{-7}$[c]	35
Serotonin + tripelennamine (3.4×10^{-7} M)	3	$3.6 \times 10^{-8} \pm 1.9 \times 10^{-8}$	3
B. Histamine (control)	5	$2.7 \times 10^{-7} \pm 1.1 \times 10^{-7}$	
Histamine + tripelennamine (3.4×10^{-7} M)	5	$1.5 \times 10^{-5} \pm 4.4 \times 10^{-6}$[c]	55
C. Bufotenine (control)	5	$5.4 \times 10^{-8} \pm 9.9 \times 10^{-9}$	
Bufotenine + cinanserin (3×10^{-7} M)	5	$3.3 \times 10^{-6} \pm 1.0 \times 10^{-6}$[c]	61
Bufotenine + tripelennamine (3.4×10^{-7} M)	5	$3.3 \times 10^{-8} \pm 1.1 \times 10^{-8}$	0.61
D. Psilocybin (control)	6	$8.2 \times 10^{-7} \pm 2.4 \times 10^{-7}$	
Psilocybin + cinanserin (3×10^{-7} M)	6	$5.2 \times 10^{-6} \pm 1.6 \times 10^{-7}$[c]	6.3
E. Psilocin (control)	6	$3.5 \times 10^{-7} \pm 1.3 \times 10^{-7}$	
Psilocin + cinanserin (3×10^{-7} M)	6	$2.9 \times 10^{-6} \pm 1.3 \times 10^{-6}$[c]	8.3
Psilocin + tripelennamine (3.4×10^{-7} M)	5	$7.7 \times 10^{-7} \pm 5.6 \times 10^{-7}$	2.2
F. Mescaline (control)	6	$8.8 \times 10^{-6} \pm 3.0 \times 10^{-6}$	
Mescaline + tripelennamine (3.4×10^{-7} M)	4	$8.6 \times 10^{-6} \pm 7.1 \times 10^{-6}$	0.98
G. Bradykinin (control)	5	$1.9 \times 10^{-9} \pm 1.0 \times 10^{-9}$	
Bradykinin + cinanserin (3×10^{-7} M)	4	$4.4 \times 10^{-9} \pm 2.5 \times 10^{-9}$	2.3

[a] *N*, number of experiments.

[b] Values given are ED50 ± S.E.M. of the concentration producing 50% of the maximum response relative to serotonin.

[c] Significantly different from the control in the respective group ($P < .05$).

TABLE 2

Sheep umbilical artery: A comparison of the concentration of various agonists required to produce a contraction equal to that obtained at the ED50 of serotonin

	N[a]	ED50 ± S.E.M.[b]	Dose-Ratio at ED50; Treated/Control
		M	
A. Serotonin (control)	9	$6.1 \times 10^{-7} \pm 1.5 \times 10^{-7}$	
Serotonin + cinanserin (3×10^{-7} M)	4	$2.9 \times 10^{-5} \pm 6.1 \times 10^{-6}$[c]	47
Serotonin + BOL (2.5×10^{-7} M)	4	$2.4 \times 10^{-4} \pm 8.3 \times 10^{-5}$[c]	393
Serotonin + atropine (1.2×10^{-7} M)	6	$8.0 \times 10^{-7} \pm 2.1 \times 10^{-7}$	1.3
Serotonin + piperoxan (3.7×10^{-7} M)	5	$1.9 \times 10^{-6} \pm 1.3 \times 10^{-6}$	3.1
Serotonin + piperoxan (3.7×10^{-6} M)	4	$3.0 \times 10^{-6} \pm 5.6 \times 10^{-7}$[c]	4.9
B. Bufotenine (control)	9	$4.4 \times 10^{-7} \pm 1.4 \times 10^{-7}$	
Bufotenine + cinanserin (3×10^{-7} M)	4	$1.5 \times 10^{-5} \pm 4.1 \times 10^{-6}$[c]	34.1
Bufotenine + piperoxan (3.7×10^{-7} M)	5	$8.7 \times 10^{-7} \pm 4.8 \times 10^{-7}$	1.9
Bufotenine + atropine (1.2×10^{-7} M)	5	$5.1 \times 10^{-7} \pm 4.0 \times 10^{-7}$	1.2
C. Mescaline (control)	4	$8.5 \times 10^{-7} \pm 1.5 \times 10^{-7}$	
Mescaline + piperoxan (3.7×10^{-6} M)	4	$4.0 \times 10^{-6} \pm 7.3 \times 10^{-7}$[c]	4.7
D. Angiotensin (control)	4	$1.0 \times 10^{-7} \pm 1.9 \times 10^{-8}$	
Angiotensin + cinanserin (3×10^{-7} M)	4	$8.8 \times 10^{-8} \pm 2.1 \times 10^{-8}$	0.9

[a] *N*, number of experiments.

[b] Values given are ED50 ± S.E.M. of the concentration of drug producing 50% of the maximum response relative to serotonin.

[c] Significantly different from the control in the respective group ($P < .05$).

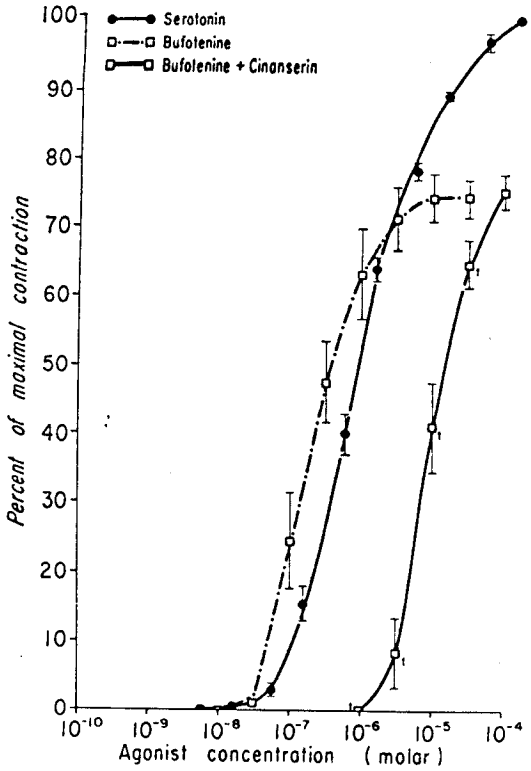

FIG. 5. Isolated sheep umbilical arteries: a comparison of the activity of bufotenine to serotonin. Bufotenine did not produce a maximal response relative to serotonin. Cinanserin hydrochloride (3×10^{-7} M) added to the bath 10 minutes prior to exposure to bufotenine shifted the dose-response to bufotenine to the right. Vertical bars represent ± S.E.M. of four experiments. †'s represent points on the cinanserin treatment curve which are significantly different from bufotenine alone ($P < .05$).

appreciably antagonize responses to angiotensin or bradykinin, thereby suggesting it is a rather specific serotonergic antagonist in our test systems. Coupled to these findings was the observation that BOL likewise antagonized responses to serotonin, LSD and mescaline on sheep umbilical arteries. These results strongly suggest that psilocin, psilocybin, bufotenine and mescaline exert their pharmacologic effect by acting on serotonergic receptors. Mescaline was not antagonized by piperoxan at concentrations which block epinephrine. Also, mescaline produced contractions on sheep umbilical arteries to 92% of the serotonin maximum, whereas epinephrine only produced contractions to 26% of the serotonin maximum. Experiments with tripelennamine suggest that histaminergic receptors are not involved in contractions to these hallucinogens. This finding is consistent with the observation that all of the hallucinogens contracted sheep umbilical arteries, a tissue insensitive to histamine (Dyer *et al.*, 1972). We conclude, therefore, that mescaline acts on serotonergic receptors and not adrenergic receptors despite its chemical resemblance to the catecholamines. Contractions to LSD were inhibited by cinanserin and BOL but not by piperoxan, atropine or tripelennamine, suggesting that LSD acts as an agonist on serotonergic receptors in umbilical vasculature.

Snyder and Richelson (1968) recently have presented evidence based on molecular orbital calculations that LSD, psilocin and mescaline

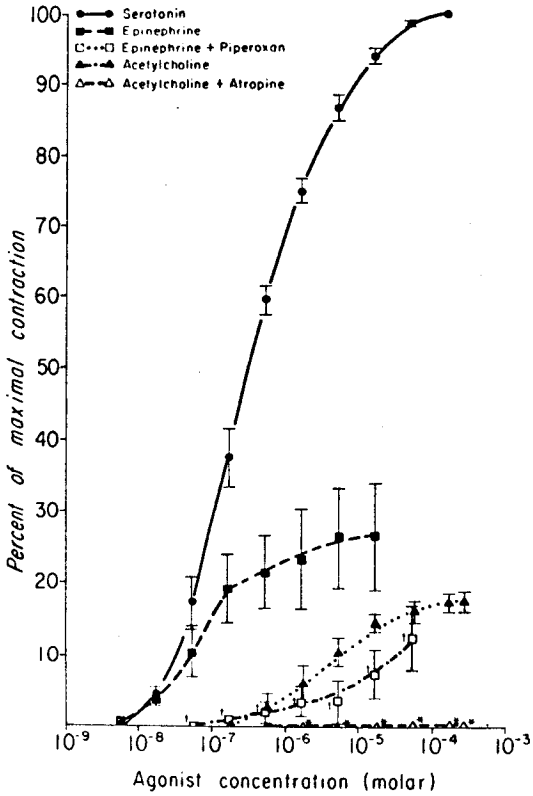

FIG. 6. Isolated sheep umbilical arteries: a comparison of the vasoconstrictor action of serotonin ($N = 9$), epinephrine ($N = 5$) and acetylcholine ($N = 4$). Neither epinephrine nor acetylcholine produced a contraction to the extent elicited by serotonin. Piperoxan (3×10^{-7} M) and atropine (1.2×10^{-7} M) were added to the baths 10 minutes prior to the addition of epinephrine or acetylcholine, respectively. Vertical bars represent ± S.E.M. †'s indicate points on the epinephrine-piperoxan curve which are significantly different from epinephrine alone whereas *'s indicate points on the acetylcholine-atropine curve which are significantly different from acetylcholine alone ($P < .05$).

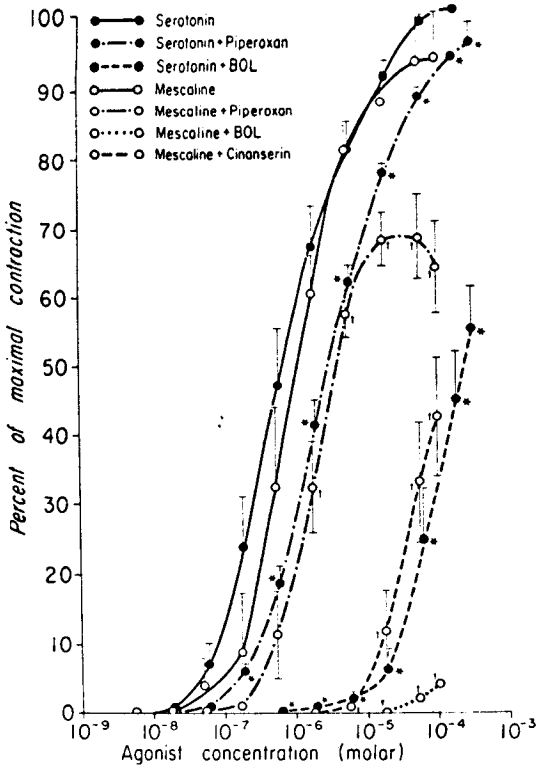

FIG. 7. Experiments were performed on isolated sheep umbilical arteries. Piperoxan hydrochloride (3.7×10^{-6} M) antagonized responses to serotonin and mescaline about equally. BOL (2.5×10^{-7} M) antagonized responses to serotonin and mescaline. Cinanserin hydrochloride (3×10^{-7} M) also antagonized responses to mescaline. Vertical bars represent ± S.E.M. of four to seven experiments. *'s indicate points on the serotonin-piperoxan curve and serotonin-BOL curve which are significantly different from serotonin alone whereas †'s indicate points on the mescaline-piperoxan, mescaline-BOL and mescaline-cinanserin curve which are significantly different from mescaline alone ($P < .05$).

may possess a common chemical configuration. This finding supports our present contention of the involvement of a common receptor site for the hallucinogens. In addition, there are a number of reports in the literature which suggest that LSD, bufotenine, psilocin, psilocybin and mescaline act on common receptors and these will be discussed below. On uterine smooth muscle, LSD in low concentrations facilitates serotonin-induced contractions whereas at higher concentrations it inhibits contractions to serotonin. Mescaline also contracted the uterus and facilitated serotonin-mediated contractions. The contractions to mescaline were antagonized by LSD (Costa, 1956).

In studies on dog blood pressure, Buñag and Walaszek (1962) observed that responses to serotonin, bufotenine, psilocin and psilocybin were antagonized by 1-benzyl-2-methyl-5-hydroxytryptamine (BAS-phenol). In a much more complex system than smooth muscle or the cardiovascular system, *i.e.*, human behavior to hallucinogenic drugs, there is evidence for cross-tolerance among the compounds we have studied. Cross-tolerance between LSD and mescaline has been reported (Balestrieri, 1957). Wolback *et al.* (1962a) compared the effects to mescaline and LSD in human volunteers. They observed similar effects on temperature, blood pressure, pupillary diameter and responses to questions when an equivalent hallucinatory dosage was given. In patients in which tolerance was developed by the chronic administration of either LSD or mesca-

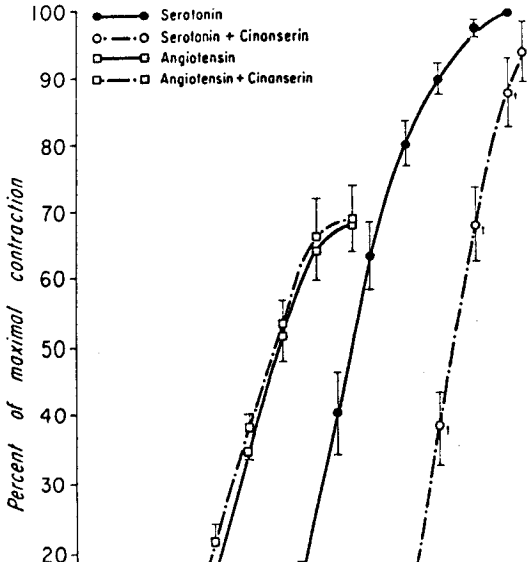

FIG. 8. Experiments demonstrating that cinanserin antagonizes responses to serotonin but not angiotensin on isolated sheep umbilical arteries. Cinanserin hydrochloride (3×10^{-7} M) was added to the bath 10 minutes prior to exposure to angiotensin or serotonin. Vertical bars represent ± S.E.M. of four experiments. †'s represent points on the serotonin-cinanserin curve which are significantly different from serotonin alone ($P < .05$).

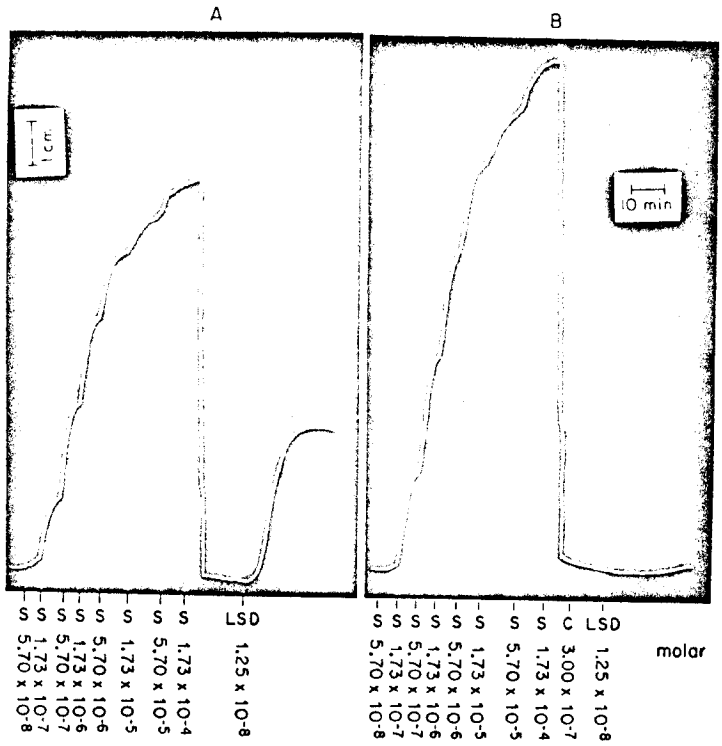

FIG. 9. Isolated sheep umbilical arteries: an experiment comparing the contractile effect to serotonin (S) and LSD on strips obtained from the same umbilical cord. Exposure of the paired tissue (panel B) to cinanserin hydrochloride (C, 3.0×10^{-7} M) for 10 minutes prior to the addition of LSD abolished the LSD-induced response. Typical of four experiments.

line, cross-tolerance occurred to the other drug. Similar comparisons of the pharmacologic activity of psilocin, psilocybin, mescaline and LSD have been made (Wolbach *et al.*, 1962b). There is also evidence suggesting that cross-tolerance occurs between LSD and psilocybin (Isbell *et al.*, 1961). The above studies strongly suggest that the autonomic effects as well as mental aberrations produced by these four drugs are similar, the only dissimilarity being the dosage required to produce equivalent biologic effects. Current thoughts as to the mechanisms by which hallucinogens may effect the central nervous system have been summarized by Hollister (1968). It is well documented that there is little correlation between hallucinatory activity and antiserotonin potency for hallucinogenic drugs (Isbell *et al.*, 1959; Hollister, 1968). There has been a great deal of excitement in the last 15 years generated by the actions of LSD on muscle. The heart of *Venus mercenaria* is very sensitive to stimulation by serotonin whereas LSD produces a stimulation which resembles that to serotonin (Shaw and

TABLE 3

Effect of antagonists on contractions elicited to a standard concentration of LSD on isolated sheep umbilical arteries

	N[a]	Percentage of Maximal Contraction (Serotonin; Mean ± S.E.M.)
LSD (1.25×10^{-8} M)	5	36.2 ± 6.1
LSD (1.25×10^{-8} M) + piperoxan (3.7×10^{-6} M)	4	37.5 ± 8.4
LSD (1.25×10^{-8} M) + BOL (2.5×10^{-7} M)	5	0[b]
LSD (1.25×10^{-8} M) + cinanserin (3×10^{-7} M)	4	0[b]
LSD (1.25×10^{-8} M) + atropine (1.2×10^{-6} M)	5	35.0 ± 9.2

[a] *N*, number of experiments.

[b] Significantly different from LSD alone ($P < .05$).

Woolley, 1956; Welsh and McCoy, 1957). However, we have no way of knowing if results obtained by others with LSD on *V. mercenaria* and in our study on vascular smooth muscle bear any relationship to the actions of these hallucinogenic compounds on the central nervous system. Are serotonergic receptors in umbilical vascular smooth muscle the same or similar to those in the central nervous system? It is tantalizing to think they are, but extensive studies will be required to resolve this point.

Another aspect of this research which deserves mention is the possible harmful effect on the fetus should a pregnant woman ingest these hallucinogens. It is conceivably possible that these hallucinogens could cross the placenta and enter the fetal circulation and thereby decrease the amount of fetal blood flowing through the placenta. The resultant increase in the fetal blood of metabolic waste products and decrease in the supply of oxygen and nutrients to an actively growing organism at critical stages of development may be decidedly harmful. This possibility is strengthened because there is evidence that LSD crosses from the maternal circulation and enters the fetal circulation in both mice (Idänpään-Heikkilä and Schoolar, 1969a) and hamsters (Idänpään-Heikkilä and Schoolar, 1969b).

Much of the thrust of investigators to date has dwelt on the concern of whether or not LSD produces chromosomal damage. The possible action of LSD altering fetal-placental blood flow has been essentially ignored. As to whether these compounds cross the human placenta in sufficient concentration to constrict umbilical blood vessels is not known. Such information may clarify the harmful action of hallucinogens on the fetus.

Acknowledgments. The authors express their gratitude to Dr. W. A. Hodson for his cooperation in obtaining some of the sheep tissues used in this study. We would also like to thank Drs. W. L. Hermann and K. Ueland and the obstetrical nursing staff of University Hospital for their cooperation in obtaining tissue specimens.

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