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Comparative actions of selected vasoactive drugs on isolated human uterine arteries

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Isolated human uterine arteries contracted to the following drugs in decreasing order of potency: norepinephrine, vasopressin, serotonin, histamine, ergonovine, and lysergic acid diethylamide. Oxytocin relaxed norepinephrine-contracted uterine arteries. Responses to serotonin were antagonized by methysergide, and those to histamine were antagonized by tripelennamine.

DRUGS MAY alter uteroplacental exchange by acting on either uterine or umbilical blood vessels as well as on uterine muscle. There are few reports in the literature concerning the actions of drugs on human uterine blood vessels. Ergonovine and norepinephrine have been reported to contract isolated human uterine arteries.[1] Boeles and co-workers[2] found that isolated human arteries contracted in response to ergonovine and vasopressin, but no quantitative comparisons were given. Gough and Dyer[3] observed that norepinephrine, angiotensin, and isoproterenol contracted human uterine arteries. In the latter study, isoproterenol and nitroglycerin also relaxed uterine artery strips in which tone had been induced. The purpose of the present study was to investigate the actions of selected vasoactive drugs to which the female patient may be exposed. The drugs used in this study may be either consumed by the patient or released from stores in the body and thereby have an action on the uterine arteries.

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Methods

Human uterine arteries were obtained from hysterectomy specimens within 2 hours of operation. The indications for performing the hysterectomies were: leiomyomas of uterus (26), prolapsed uteri (12), carcinoma of uterus (1), adenomyosis of uterus (9), chronic cervicitis (2), and menorrhagia and metrorrhagia (5). In this study 44 per cent of the tissues were obtained from patients who were not receiving any long-term medication, 16 per cent were receiving estrogen, 16 per cent were being treated with a thyroid hormone, 14 per cent were ingesting sedatives or tranquilizers, 12 per cent were receiving various iron preparations, 2 per cent were receiving diuretic therapy, and for 7 per cent the medication was uncertain.

The tissues were placed in Krebs-Henseleit solution containing 10 μg per milliliter of disodium ethylenediaminetetra-acetic acid and transported to the laboratory. The arteries were trimmed of excess tissue and cut in a helical manner according to the method of Furchgott.[4] The tissues were suspended under 1 Gm. tension in a 10 ml. organ bath maintained at 37° C. and aerated with a 95 per cent O_2 and 5 per cent CO_2 mixture. Muscle activity was magnified tenfold and recorded on a kymograph. The tissues were allowed to equilibrate in the bath for at least

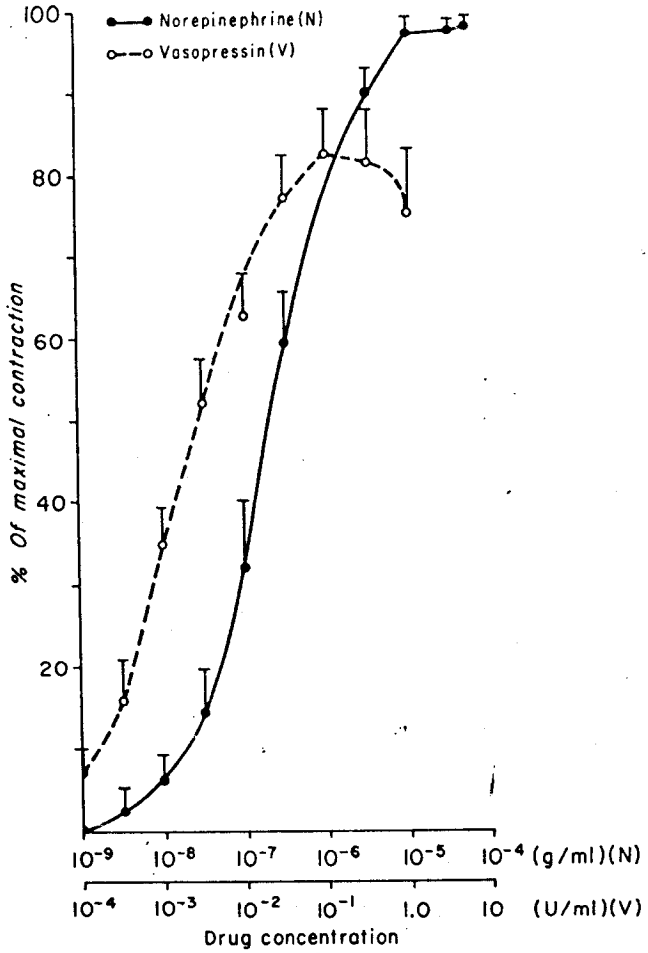

Fig. 1. Comparison of dose-response curves to norepinephrine and vasopressin. The vertical bars represent standard errors of 10 experiments.

one hour before starting of the experiment. All drug agonists were introduced into the organ bath in cumulative amounts by micropipettes. The following drugs were used in this study: *l*-norepinephrine, ergonovine maleate, vasopressin,* oxytocin,† lysergic acid diethylamide tartrate, histamine, methysergide maleate,‡ and tripelennamine hydrochloride.§

Results

The effect of the hormonal state of the uterus on the sensitivity of the uterine arteries to norepinephrine. The per cent of the maximum contraction to norepinephrine (30 ng. per milliliter) of uterine arteries taken from uteri in which the endometrium was in the secretory phase (19) and in the proliferative phase (20) was compared. There was no difference in the sensitivity of the uterine arteries to norepinephrine which correlated with the state of the endometrium.

Responses to vasopressin and oxytocin. Vasopressin contracted human uterine arteries (Fig. 1). However, the maximal tissue contraction to vasopressin was about 82 per cent of that produced to norepinephrine. Oxytocin produced small relaxations of the fully equilibrated arteries. Because the arteries exhibited little tone, it was difficult to study the relaxations produced to oxytocin.

*Pitressin, Parke, Davis & Co., Detroit, Michigan.

†Syntocinon, Sandoz Pharmaceuticals, Hanover, New Jersey.

‡Sansert, Sandoz Pharmaceuticals, Hanover, New Jersey.

§Pyribenzamine, Ciba Pharm. Products, Inc., Summit, New Jersey.

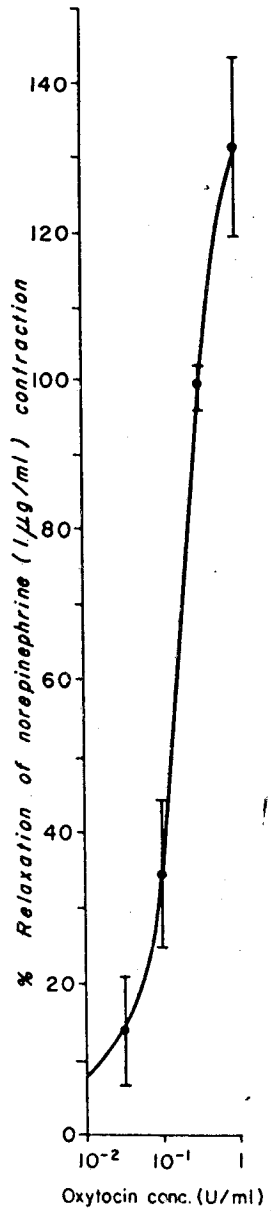

Fig. 2. Relaxation of norepinephrine-contracted uterine artery strips by oxytocin. The norepinephrine (1 µg per milliliter) was added to the Krebs solution to induce the tone. The relaxation of greater than 100 per cent indicates relaxation below the base line before the norepinephrine was added to the Krebs solution.

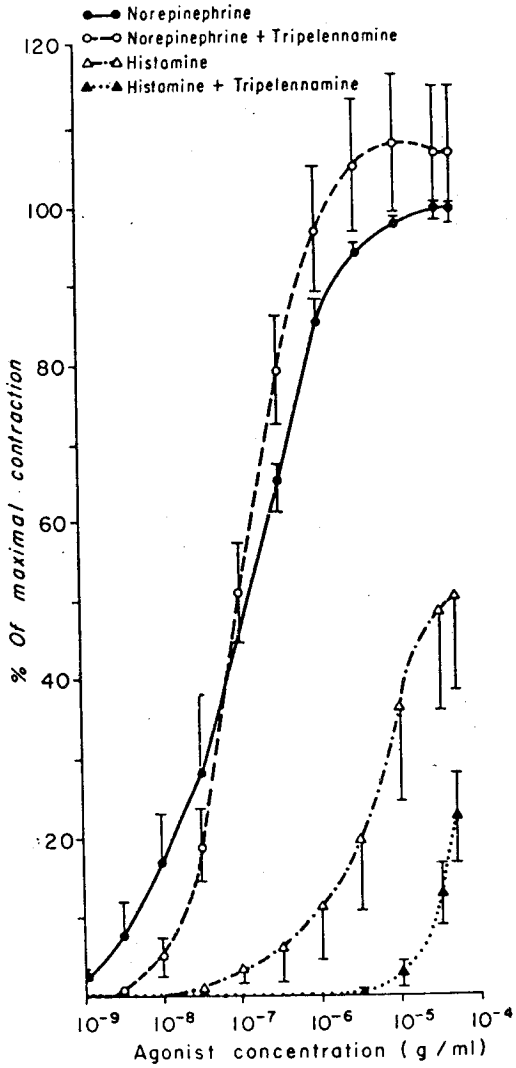

Fig. 3. Dose-response curves to norepinephrine and histamine alone and in the presence of tripelennamine. The tripelennamine (0.1 µg per milliliter) was incubated with the uterine artery strip for 15 minutes before repeating the second dose-response experiment to histamine or norepinephrine. Tripelennamine had little action on responses to norepinephrine but did competitively antagonize responses to histamine. The vertical bars represent the standard errors of 7 experiments.

To overcome this difficulty, norepinephrine (1 µg per milliliter) was added to the Krebs solution to induce tone. Oxytocin relaxed the norepinephrine-contracted strips in a dose-dependent manner (Fig. 2). The greater than 100 per cent relaxation indicates relaxation below the original base line, i.e., the base line before the norepinephrine was added to the Krebs solution.

The effects of histamine and serotonin. Histamine contracted uterine arteries (Fig. 3). Relaxations to histamine in a fully equilibrated preparation did not occur. The contractions with histamine were antagonized by

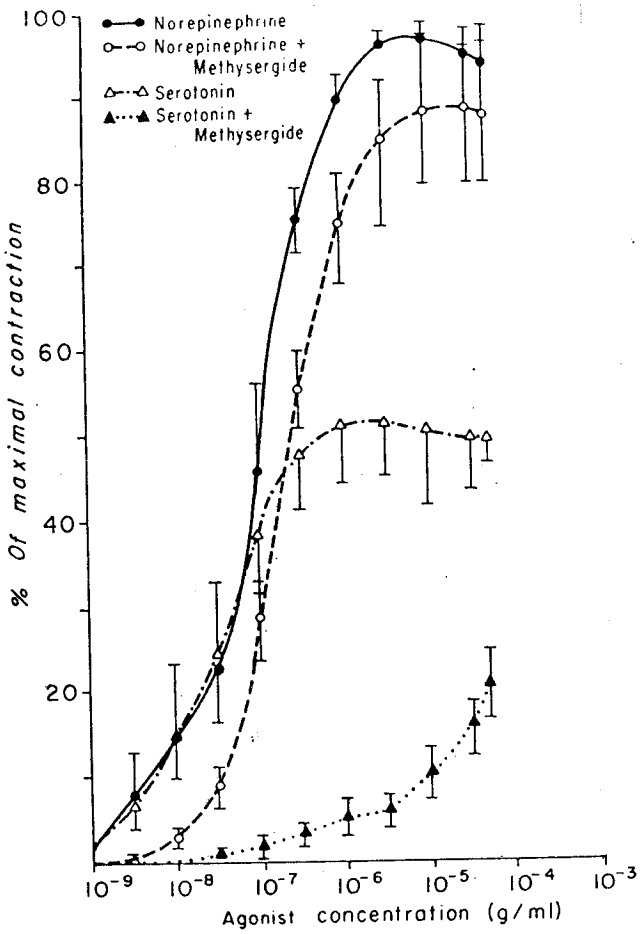

Fig. 4. The vasoconstrictor effect of norepinephrine compared to that of serotonin. Human arteries were equally sensitive to both norepinephrine and serotonin at the lower concentrations. Note the selective antagonism of serotonin by methysergide. The methysergide (0.1 μg per milliliter) was incubated with the uterine artery strip for 15 minutes before repeating the second dose-response experiment to serotonin or norepinephrine. The vertical bars represent the standard errors of 6 experiments.

tripelennamine. Tripelennamine had little action on responses to norepinephrine, thus indicating its specificity.

Serotonin produced contractions of uterine arteries with the maximum contraction obtained about the ED_{50} of that with norepinephrine (Fig. 4). Methysergide, a serotonin antagonist, blocked the responses to serotonin and had little effect on response to norepinephrine.

Responses to ergot alkaloids. A comparison of the dose-response curves obtained with ergonovine and norepinephrine is presented in Fig. 5. It is quite evident that norepinephrine produced greater contractions than did ergonovine. The maximal contraction to ergonovine reached about 30 per cent of that produced with norepinephrine.

Lysergic acid diethylamide (LSD), a hallucinogen closely related to ergonovine in chemical structure, also contracted uterine arteries, but the maximum contraction obtained was only about 20 per cent of that produced to norepinephrine (Fig. 6).

Comment

The results of the present study indicated that norepinephrine as well as vasopressin was a good agonist of human uterine arteries. The potency of vasopressin approximated

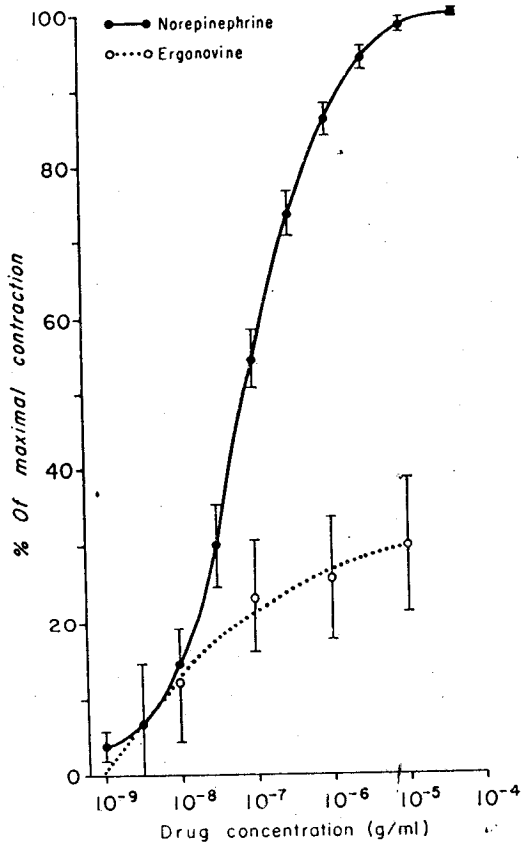

Fig. 5. Comparison of the dose-response curves of norepinephrine and ergonovine on human uterine arteries. The vertical bars represent the standard errors of 11 experiments. Drug concentrations are in grams per milliliter of Krebs solution.

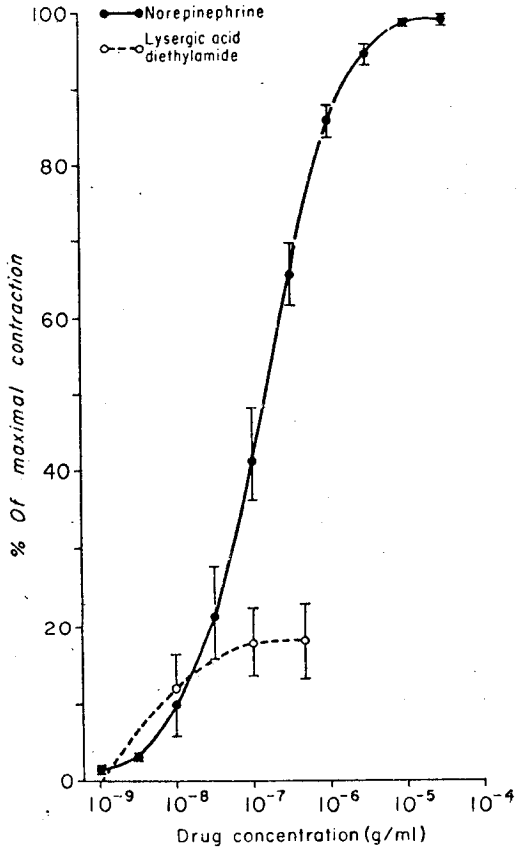

Fig. 6. Comparison of the dose-response curves of norepinephrine and lysergic acid diethylamide (LSD). The vertical bars represent the standard errors of 16 experiments. Drug concentrations are in grams per milliliter of Krebs solution.

that seen with norepinephrine. Vasopressin has been reported to constrict gastrointestinal and coronary blood vessels[5] and to decrease uterine blood flow in rabbits.[6] In the latter study, the dose of vasopressin required to reduce uterine blood flow was quite large. But, the decrease in uterine blood flow still persisted after the systemic blood pressure had returned to control levels.

Oxytocin did not produce contractions at any concentration studied but did relax uterine arteries. Compared to our previous experiments with the use of isoproterenol and nitroglycerin,[3] oxytocin produced greater relaxation of the norepinephrine-contracted arteries. It is doubtful if oxytocin relaxes uterine arteries under physiologic conditions since the maximal blood concentration reached during normal parturition was estimated to be about 20 to 40 mU. per liter.[7] Cutchin and co-workers[1] observed little or no effect of oxytocin on human uterine arteries. However, their preparations as with ours probably exhibited little tone, and, therefore, relaxation with oxytocin was not observed.

Serotonin has primarily excitatory actions on vascular tissue.[8] In the present study, serotonin constricted uterine arteries. It was interesting that at the lower concentrations serotonin and norepinephrine were equally active. The maximal contraction to serotonin was about the ED_{50} for norepinephrine. Methysergide selectively antagonized responses to serotonin over those to norepinephrine. These results indicated that serotonin acts on its own tryptamine receptors and probably not on α-adrenergic receptors. Innes[9] has presented evidence that serotonin

may act on adrenergic receptors in some tissues.

Histamine at rather large concentrations contracted uterine arteries, and these contractions were antagonized by the antihistaminic tripelennamine. Tripelennamine did not alter the ED_{50} of norepinephrine but did reduce the maximum contraction.

The ergot alkaloids are well known for their oxytocic action on the uterus. Boeles and co-workers[2] observed that ergonovine contracted human uterine arteries but did not provide good comparative drug data. In our study, ergonovine also constricted uterine arteries but was not as effective as norepinephrine. LSD, an ergot alkaloid closely related chemically to ergonovine, also constricted uterine arteries but was not as active as ergonovine. Ergonovine and ergotamine acting on sheep umbilical blood vessels[10] and LSD acting on the human umbilical vein[11] produced contractions at very low concentrations. LSD was some tenfold more active on isolated human umbilical veins than serotonin.[11] The potential cardiovascular actions of LSD are usually not discussed when considering its action on the fetus. Our present results would suggest that LSD probably has little action on uterine blood vessels. However, if LSD crossed into the fetal circulation, it might cause a pronounced decrease in uteroplacental exchange of oxygen, nutrients, and waste products by constricting umbilical vessels.

In the present study of human uterine arteries, an in vitro technique was used. Therefore, some caution may be necessary before extrapolating these data to the in vivo situation.

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REFERENCES

1. Cutchin, J. H., McGaughey, H. D., Scoggin, W. A., Harbert, G. M., and Thornton, W. N.: Am. J. Obstet. Gynecol. 90: 143, 1964.
2. Boeles, J., Lankhorst, G. J., Beuningh, H., Stobbelaar, A. K., and Zuyderhoudr, F.: Proc. Int. Union Physiol. Sci. 7: 1968.
3. Gough, E. D., and Dyer, D. C.: Am. J. Obstet. Gynecol. 110: 625, 1971.
4. Furchgott, R. F.: *In* Bruner, H. D., editor: Methods in Medical Research, Chicago, 1960, Vol. 8, Year Book Medical Publishers, Inc., pp. 177-186.
5. Somlyo, A. P., and Somlyo, A. V.: Pharmacol. Rev. 22: 249, 1970.
6. Carter, A. M., Lewis, P. J., and Bengtsson, L. P.: Acta Pharmacol. Toxicol. 24: 435, 1966.
7. Caldeyro-Barcia, R., and Poseiro, J. J.: Ann. N. Y. Acad. Sci. 75: 813, 1959.
8. Douglas, W. W.: *In* Goodman, L. S., and Gilman, A., editors: The Pharmacological Basis of Therapeutics, ed. 4, New York, 1970, The Macmillan Company, p. 647.
9. Innes, I. R.: Br. J. Pharmacol. 19: 427, 1962.
10. Dyer, D. C.: J. Pharmacol. Exp. Ther. 175: 565, 1970.
11. Gant, D. W., and Dyer, D. C.: Life Sci. 10: 235, 1971.