Life Sci. 10/I, 235-240 (1971). LSD 2138

Life Sciences Vol. 10, Part I, pp. 235-240, 1971. Pergamon Press
Printed in Great Britain

d-LYSERGIC ACID DIETHYLAMIDE (LSD-25): A CONSTRICTOR OF HUMAN UMBILICAL VEIN

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(Received 22 July 1970; in final form 4 January 1971)

Because of the number of different drugs that the gravid female is exposed to during pregnancy, it has become increasingly important to look at these drugs as they affect the mother and the fetus. Drugs possessing an action on the cardiovascular system may alter existing physiological functions. A decrease in uterine and placental blood flow could alter oxygenation and nutrition of the fetus. It is documented in the literature that serotonin is a potent constrictor of human umbilical and placental vascular smooth muscle (1, 2, 3). Eliasson and Åström (1) observed that dihydroergotamine constricted perfused human placental vessels. Dyer (4) reported that sheep umbilical blood vessels were contracted by serotonin, ergotamine, and ergonovine. d-Lysergic acid diethylamide (LSD-25) which closely resembles serotonin and the ergot alkaloids in chemical structure was used by Åström and Samelius (2) as a serotonin antagonist in studies on the perfused human placenta. In their experiments, LSD-25 increased the perfusion pressure and blocked responses to serotonin, but no quantitative analysis was made of the agonistic action of LSD-25. Because of these studies it was felt that LSD-25 should be tested for possible contractile properties on human umbilical vascular smooth muscle and its effect quantitatively and qualitatively compared to serotonin.

Methods

Umbilical cords were obtained within 40 minutes after normal deliveries and placed in modified Krebs-Henseleit (5) (Krebs) solution. The umbilical vein was dissected free from the arteries and as much of the supportive tissue as possible was removed. Eight helical strips of umbilical vein approximately

2 cm long and 0.2-0.3 cm wide were cut from each cord and placed in a series of muscle baths under one gram tension. Tissues which were not employed immediately were stored at 4°C and used within 18 hours. The tissues were equilibrated under tension for 1.5-2 hours in Krebs solution at 37°C and constantly aerated with 5% CO_2-95% O_2. Isotonic contractions were magnified tenfold and recorded on a kymograph. This technique allows for a direct comparison of drug responses with similar laboratory animal preparations by utilizing the standard conditions described by Furchgott for helically cut strips of rabbit aorta (6). Several single doses of serotonin were administered at the beginning of each experiment to insure the activity and reproducibility of the individual preparations. Cumulative dose-responses to serotonin were obtained on all preparations and the tissues were washed with fresh Krebs solution after the maximal contraction was reached. After relaxation, a single concentration of LSD-25 was added to each tissue bath to establish a dose-response relationship by expressing the contraction as a percent of the maximal response elicited by serotonin.

In another series of experiments, after obtaining control responses to serotonin, phenoxybenzamine (10^{-6} gm/ml) was added to the bath and allowed to remain in contact with the tissues for ten minutes. The phenoxybenzamine was then flushed out of the bath and the tissues washed intermittently for a period of thirty minutes. LSD-25 and serotonin were added to these preparations to test for antagonism by phenoxybenzamine.

Results

An experiment demonstrating the effect of serotonin and LSD-25 on four helical strips from one umbilical cord is presented in Figure 1. Of interest was the prolonged lag before the initiation of contraction to LSD-25 and also the irregularity of the contractile response at the lower concentrations. Contrast these observations to the higher concentrations of LSD-25 which produced a more rapid contraction that was held relatively constant with time. Control tissues showed little alteration in the responsiveness to serotonin over a four hour period. Once LSD-25 was added to a preparation and a contraction recorded,

it was extremely difficult to get the tissue to relax back to the base line, even with repeated changing of the bathing fluid.

A comparison of the dose-response curves of serotonin and LSD-25 is presented in Figure 2. The maximum contractile effect produced by LSD-25 was less than that to serotonin, reaching approximately 90% of the serotonin response. But, in the lower concentration range, LSD-25 (10^{-10} - 10^{-8} gm/ml) produced larger contractions than serotonin. From these data it seems apparent that human umbilical vein possesses a greater sensitivity to LSD-25 (i.e., requires less drug to evoke a response) than to serotonin. The studies utilizing phenoxybenzamine are also presented in Figure 2. Phenoxybenzamine decreased the maximum contractile effect to both drugs. The dose-response curve at 50% maximal contraction was shifted to the right over 7-fold for serotonin and 20-fold for LSD-25.

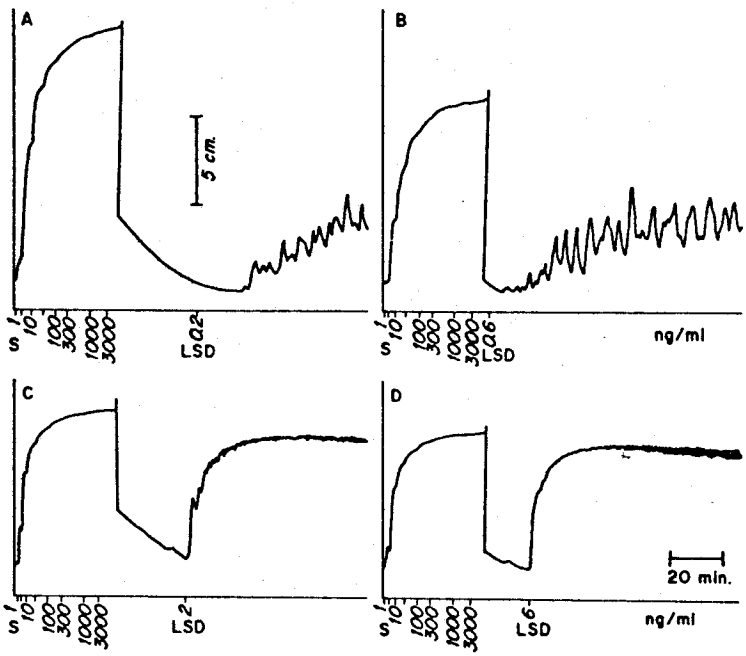

FIG. 1

Isolated human umbilical vein: Four preparations cut from the same cord. A cumulative dose-response to serotonin (S) preceded the addition of LSD-25. The following concentrations of LSD-25 were used: In panel A: 0.2 ng/ml; in panel B: 0.6 ng/ml; in panel C: 2 ng/ml; and in panel D: 6 ng/ml.

It should be pointed out that a cumulative dose-response to LSD-25 could not be obtained on individual tissues. That is, when increasing amounts of LSD-25 were added to the bath without changing the fluid, larger contractions were not produced. This observation may be related to the phenomenon of auto-inhibition and is supported by the observation that ergotamine, another closely related ergot alkaloid, will block its own contractile effect (7). This problem was overcome by adding a different dose of LSD-25 to each tissue.

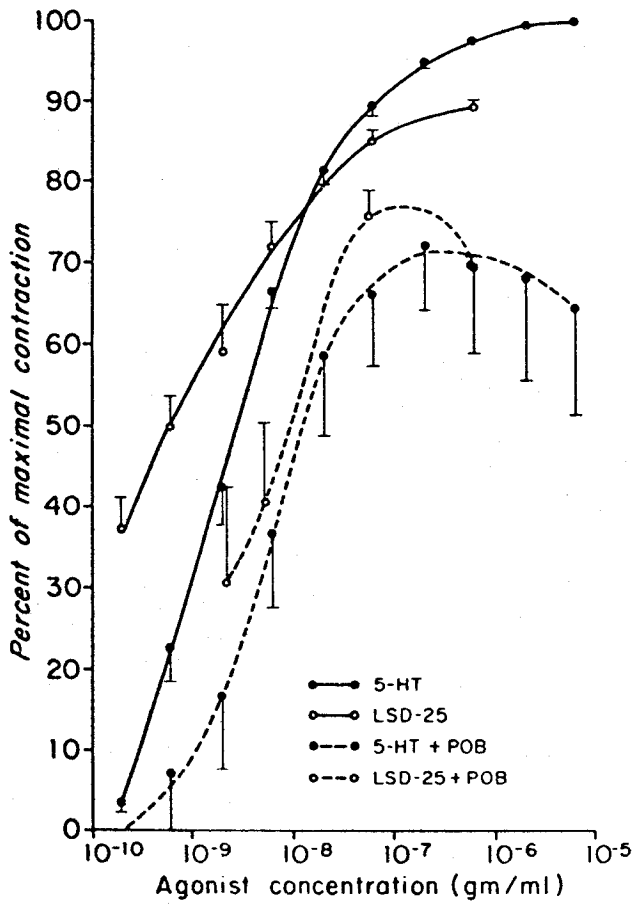

FIG. 2

A comparison of the dose-response curves to serotonin (5-HT) and LSD-25 and the antagonism by phenoxybenzamine (POB). Vertical bars represent standard errors.

Although the results of these experiments were obtained under conditions of high oxygen tension, comparable results have been obtained with low pO_2 values (<15 mm Hg) by aerating the Krebs solution with 95% N_2-5% CO_2 (12).

Discussion

Murphree (8) reported that phenoxybenzamine antagonized the central nervous system effects of LSD-25. Although more work needs to be done in this area, it appears that phenoxybenzamine could be used to antagonize central and peripheral actions of LSD-25. The contractile action of LSD-25 on human umbilical vein may take on added clinical importance since Heikkilä and Schoolar have recently demonstrated that LSD-25 crosses the placenta from the maternal circulation and enters the fetal circulation in both gravid mice (9) and hamsters (10). The significance of these studies cannot be fully evaluated since there is such a large variation in the half-life of LSD-25 in mice (7 minutes) versus man (175 minutes) (11). Aghajanian and Bing (11) have also shown in humans that four hours following a 2 µg/kg i.v. injection of LSD-25, a plasma level of 3 ng/ml could be detected. This concentration of LSD-25 produced a strong contraction of isolated human umbilical vein in our study.

Summary

In summary, experiments on isolated human umbilical vein indicated both serotonin and LSD-25 to be potent vasoconstrictors. The contractile response to LSD-25 was more persistent than to serotonin. In the lower concentration range, which may be more important clinically, LSD-25 was more potent than serotonin.

In view of the current abuse of LSD-25, the results of our study may hint to possible toxic effects of LSD-25 on the fetus *in utero*. Our hypothesis is that upon crossing the placental barrier into the fetal circulation, LSD-25 could constrict the umbilical blood vessels. The constriction would result in a decreased fetal blood flow through the placenta which may cause fetal hypoxia and its potentially harmful consequences.

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5. Composition: NaCl 6.74, KCl 0.35, $CaCl_2$ 0.20, $MgSO_4$ 0.14, KH_2PO_4 0.16, NA_2(EDTA) 0.01, $NaHCO_3$ 1.86, Dextrose 1.42 (gm/l).

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13. Supported by NIH Grant No. GM15991 and by PHS Training Grant No. GM01458 from the National Institute of General Medical Sciences. We thank Drs. W.L. Hermann, W. Heinrichs and K. Ueland and the obstetrical nursing staff of the University of Washington Hospital for cooperation in obtaining tissue specimens. The data in this publication will be submitted by D.W.G. in partial fulfillment of the requirements for the degree of Master of Science.