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Antidiuretic Effect of Lysergic Acid Diethylamide in Humans

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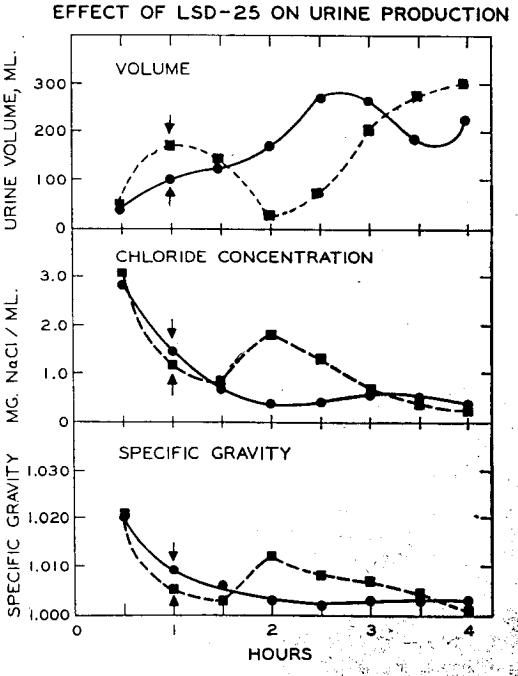
In the years following the first clinical report on the effects of lysergic acid diethylamide [1] many publications have described both the psychological and the physiological alterations produced in human subjects by LSD. Although its site of action has not been established, there has been considerable speculation that some of the psychological effects of LSD are related to hypothalamic stimulation. Since one effect of hypothalamic stimulation is increased production of antidiuretic hormone,[2] the assumption that LSD acts by stimulating the hypothalamus would carry the prediction that LSD should have antidiuretic properties. The data to be described demonstrate that LSD has strong antidiuretic effects; these data are consistent with the notion that hypothalamic stimulation may be related to certain of the psychological effects of LSD.

Experimental Study

The subjects were seven healthy male subjects, ranging in age from 19 to 29 years, who were given lysergic acid diethylamide in connection with psychological studies made in our laboratory. No food was given after 8 o'clock on the evening before each experimental period, although water was allowed ad libitum. At 8 a. m. on the day of an experiment the bladder was emptied and 200 ml. of tap water was ingested. Thereafter, the bladder was emptied and 200 ml. of water administered every half-hour until the end of the four-hour experimental period. One hour after the beginning of the experiment the subjects were given an intravenous injection of 100γ of LSD-25 in 1 ml. of saline or a placebo of 1 ml. of saline. The subjects were instructed to sit quietly, or recline, with a minimum of muscular exertion.

The urine volumes for each half-hour period were measured and the chloride concentration determined by the Volhard-Harvey method, as described in Hawk, Oser, and Summerson.[3] There were 19 control experiments and 14 experiments in which subjects received LSD-25.

The effect of the intravenous LSD-25 on the urine volume of hydrated subjects is shown in the Figure. There is a marked antidiuresis, which is apparent one hour



Effect of intravenous injection of lysergic acid diethylamide (LSD-25) on urine volume, chloride concentration, and specific gravity in hydrated human subject. Arrows indicate time of injection of either 1 ml. of isotonic saline (solid lines) or 100γ of LSD-25 in 1 ml. of isotonic saline (broken lines).

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after the injection of the LSD-25 and which lasts for one hour. Later, there is an increased urine output as compared with the corresponding control periods. Although there was considerable variation in both the control values and the individual responses to the drugs, the antidiuretic effect of LSD-25 during the fourth and fifth collection periods (one and one and one-half hours after administration) was highly significant ($P = <0.01$). The subsequent increase in urine production of the subjects receiving LSD-25 was significantly different from the controls only during the eighth period.

LSD also exerts an effect on the urine chloride concentration. Although LSD did not significantly alter the total chloride excretion, the effect of the drug was evident in the increased chloride content of the urine voided one to one and one-half hours after injection.

Comment

The mechanism whereby the administration of LSD-25 in hydrated subjects produces an antidiuretic effect is not known. One may speculate, however, that this physiological response to LSD-25 is the result of antidiuretic hormone (ADH) liberation which follows hypothalamic stimulation by LSD. The pattern of urine suppression, with corresponding increase in chloride concentration, is similar to the effects of anoxic painful stimuli in man observed by Kelsall [4] and Mirsky and Stein.[5] These authors used a physical stress which they believed stimulated the hypothalamus to release increased amounts of the antidiuretic hormone. In our experiments, LSD-25 may have constituted a chemical stress. There is one important difference between the antidiuretic effects of painful stimuli and those of LSD. In the experiments reported here the antidiuretic response to LSD was considerably delayed (more than one-half hour), whereas the antidiuretic response to physical stress reported by Mirsky and others was apparent within 10 minutes. This delay in the antidiuretic response to LSD is in contrast to the psychic effects of the drug, which in these subjects were demonstrable in 5 to 10 minutes. It may be that the hypothalamic stimulation postulated is itself a secondary effect, arising from the effects of LSD-25 on other central nervous system structures.

Erspamer [6] has shown that the antidiuretic effects of serotonin in the rat are inhibited by LSD. This antidiuresis is explained by Rothlin et al.[7] in terms of the effect of serotonin on renal blood flow. Although LSD has no marked effect on renal blood flow under the specific experimental conditions cited, it inhibits the action of serotonin. It should be pointed out that the antidiuresis reported here is dissimilar to the antidiuretic action of serotonin and that there is no inconsistency in the two reports.

Summary

LSD administered to hydrated male adults exerts a marked antidiuretic action, which begins approximately one-half hour after intravenous injection of the drug and whose duration is roughly one hour. Thereafter, an increased urine output compensates for the excess water retained by the body during the antidiuresis. It is suggested that this effect of LSD may be the result of hypothalamic stimulation, although the experimental data do not exclude other possible explanations.

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REFERENCES

1. Stoll, W. A.: Lysergsäure-diäthyl-amid, ein Phantastikum aus der Mutterkorngruppe, Schweiz. Arch. Neurol. u. Psychiat. 60:279-323, 1947.

2. Mirsky, I. A.; Stein, M., and Paulisch, G.: Secretion of an Antidiuretic Substance into the Circulation of Adrenalectomized and Hypophysectomized Rats Exposed to Noxious Stimuli, Endocrinology 55:28-39, 1954.

3. Hawk, P. B.; Oser, B. L., and Summerson, W. H.: Practical Physiological Chemistry, Ed. 13, New York, The Blakiston Division, McGraw-Hill Book Company, Inc., 1954, p. 956.

4. Kelsall, A. R.: Inhibition of Water Diure-
Activity of the Blood, Science 118:602-603, 1953.
sis in Man by Ischaemic Muscle Pain, J. Physiol. 109:150-161, 1949.

5. Mirsky, I. A., and Stein, M.: Effect of a Noxious Stimulus in Man on the Antidiuretic Activity of the Blood, Science 118:602-603, 1953.

6. Erspamer, V.: Il sistema cellulare entero-cromaffine e l'enteramina (5-idrossitriptamina), Rendic. sc. farmital. 1:1-178, 1954.

7. Rothlin, E.; Carpi, A., and Cerletti, A.: Studi sull'attività vascolare dell'enteramina, Atti XVI Congr. Soc. ital. cardiol., June, 1954 pp. 379-383.

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