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Department of Physiology, School of Medicine,
University of California Medical Center, San Francisco 22,
California, U. S. A.

EFFECT OF LYSERGIC ACID DIETHYLAMIDE ON ADRENOCORTICAL AND ADRENAL MEDULLARY FUNCTION IN THE DOG

By

William F. Ganong, Alan Goldfien, Al Halevy, Julian M. Davidson and Angela Boryczka

ABSTRACT

The effect of lysergic acid diethylamide (LSD) on adrenal cortical and medullary function in anaesthetized dogs has been determined by measuring the output of 17-hydroxycorticoids and epinephrine and norepinephrine in the adrenal vein before and after the administration of 50 μg/kg of LSD or control injections of saline. A slight rise in 17-hydroxycorticoid secretion was observed following LSD administration; epinephrine and norepinephrine secretion values did not differ significantly from the low values found in the controls. The increase in 17-hydroxycorticoid secretion produced by a subsequent laparotomy and the administration of corticotrophin was unaffected by LSD.

There is considerable difference of opinion about the effects of lysergic acid diethylamide (LSD) on adrenocortical function (*Hoagland et al.* 1955; *Rinkel et al.* 1955; *Nadel et al.* 1957; *Lingjærde & Skaug* 1956), and its effect on adrenal medullary secretion has not been measured directly, although it is said to increase sympathetic activity (*Rothlin* 1957; *Graham & Khalide* 1954). In the present experiments, the effect of LSD on adrenal cortical and medullary function has been determined by measuring the output of 17-hydroxycorticoids and catechol amines in the adrenal venous blood of anaesthetized dogs.

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METHODS

13 pentobarbital-anaesthetized male mongrel dogs weighing 8.0–16.2 kg were used. The right or left adrenal vein was cannulated by the technique of *Hume & Nelson* (1955). Plastic cannulae were also placed in the femoral vein for injecting drugs, and the femoral artery for monitoring blood pressure with a mercury manometer. Six hours after the acute surgical stress of cannulation, LSD was administered intravenously. Seven dogs received 50 μg/kg, and one was given 200 μg/kg. Six dogs received a control injection of isotonic saline. Adrenal venous blood samples were obtained immediately before, and in most cases, 5, 15, 30, and 55–65 minutes after LSD or saline administration. A laparotomy was then performed and adrenal venous blood collected 15 and 30 minutes after this stress. 35 min after laparotomy, the animals were given one IU of corticotrophin (ACTH) intravenously and an adrenal venous blood sample obtained starting four minutes after the injection. All samples were centrifuged promptly and the plasma separated and frozen for subsequent chemical analysis. 17-hydroxycorticoids were determined by the method of *Silber & Porter* (1954). Epinephrine and norepinephrine were measured by a modification of the ethylenediamine technique (*Goldfien et al.*, in press). The output per minute of each of these hormones was calculated by multiplying their concentration in adrenal venous plasma by the adrenal venous plasma flow per minute.

RESULTS

The dog receiving 200 μg/kg of LSD died within three minutes after the injection. A dose of 50 μg/kg had no definite effect on the general condition of the dogs. Blood pressure was not consistently changed. Depth of anaesthesia seemed unaffected, although no detailed observations of this parameter were made.

Table 1.
Effect of LSD on adrenocortical function.

	17-hydroxycorticoid output (μg/min)	
	LSD 50 μg/kg	Saline
before injection	5.3 ± 1.6 (7)	2.8 ± 0.5 (6)
5 min after injection	5.5 ± 1.7 (4)	3.6 ± 1.0 (5)
15 „ „ „	8.0 ± 1.8 (7)	4.3 ± 0.9 (6)
30 „ „ „	8.9 ± 1.7 (7)	5.1 ± 0.8 (6)
55–65 „ „	5.0 ± 2.1 (7)	6.4 ± 1.1 (5)
15 „ „ laparotomy	10.6 ± 2.2 (6)	7.7 ± 1.4 (6)
30 „ „ „	10.8 ± 2.4 (5)	8.2 ± 1.5 (6)
4 „ „ 1 IU ACTH	12.8 ± 2.6 (5)	8.6 ± 0.8 (6)

Values are means ± standard error. Figures in parentheses are number of animals for that determination.

Table 2.
Effect of LSD on adrenal medullary function.

	Epinephrine and norepinephrine output (ng/min)					
	LSD 50 μg/kg			Saline		
	Epi.	Norepi.	N	Epi.	Norepi.	N
before injection	15.2 ± 5.5	9.6 ± 2.9	6	19.2 ± 7.1	10.1 ± 2.7	6
5 min after injection	3.9 ± 1.6	31.1 ± 18.9	3	10.9 ± 3.4	9.7 ± 3.5	4
15 „ „ „	18.0 ± 6.6	26.8 ± 11.1	6	24.0 ± 9.2	17.0 ± 6.7	6
30 „ „ „	14.8 ± 5.1	21.0 ± 6.9	6	14.2 ± 6.7	4.0 ± 2.0	3
55–65 „ „	15.9 ± 5.0	19.4 ± 7.9	6	11.4 ± 4.3	13.8 ± 3.2	3
15 „ „ laparotomy	14.2 ± 6.1	19.4 ± 11.3	4	14.4 ± 7.7	11.8 ± 3.6	4
30 „ „ „	18.4 ± 7.0	22.5 ± 12.7	4	65.4 ± 39.5	18.3 ± 10.0	3
4 „ „ „	25.2 ± 9.2	28.2 ± 15.6	4	33.7 ± 20.3	11.6 ± 5.9	4

Values are means ± standard error. N = number of animals for that determination.

The data on adrenocortical hormone output are summarized in Table 1. Before LSD administration, mean 17-hydroxycorticoid output values were about 1/3 the subsequent maximum output obtained with ACTH. Following LSD administration output rose moderately, and then declined. The mean values in the LSD-treated dogs 15 and 30 minutes after LSD administration are not significantly greater than the comparable values in saline treated controls. 15 and 30 minutes after laparotomy, 17-hydroxycorticoid output was increased in both groups of animals, and a further slight rise followed ACTH administration. The slightly higher mean values in the LSD-treated dogs after laparotomy and ACTH are not significantly different from those in the saline injected dogs.

The number of dogs in which epinephrine and norepinephrine secretion was measured at each time interval and the mean values obtained are shown in Table 2. Epinephrine secretion fluctuated somewhat from dog to dog in both LSD and control groups, but there was no consistent change after LSD administration. Following laparotomy, increased secretion occurred in two of the four control dogs in which it was measured, but did not occur in the four LSD-treated dogs studied. Norepinephrine secretion increased after LSD administration in five of the six dogs studied, but the mean norepinephrine values are not significantly different from control means during any of the collection periods.

DISCUSSION

Six hours after the stress of adrenal cannulation, before injection of LSD or saline, 17-hydroxycorticoid secretion had fallen considerably. However, it had not reached the basal values of 0–2 μg/min found in unstressed dogs (*Nelson et al.* 1956). The fluctuation in 17-hydroxycorticoid secretion in some of the control dogs during the hour after saline injection was unrelated to any discernible experimental variable. These fluctuations would tend to obscure any adrenocortical stimulation due to LSD. Somewhat similar transient and unexplained variation in secretion was observed by *Nelson et al.* (1956) in dogs 24 hours after adrenal vein cannulation. On the other hand, 17-hydroxycorticoid secretion increased uniformly after laparotomy and ACTH administration, and therefore any inhibition of secretion by LSD would have been clearly shown. The magnitude of the rise following the laparotomy performed seven hours after cannulation is similar to the rise found after laparotomy in previously unstressed dogs under pentobarbital anaesthesia (*Ganong* 1959).

Rinkel et al. (1955) and *Hoagland et al.* (1955) suggested that LSD inhibited the adrenocortical response to stress, although it could act as a stressor itself. This conclusion was based on the observation that LSD caused a decrease in urinary phosphate excretion, while ACTH administration caused a rise. The administration of LSD followed by ACTH caused a lesser rise in phosphate excretion than did ACTH alone, suggesting that the response to ACTH was diminished. Similar results were subsequently reported by *Bergen & Beisaw* (1956). LSD is an antagonist to serotonin, at least in several peripheral tissues, and serotonin is known to cause ACTH discharge with consequent increased adrenocortical secretion (*Erspamer* 1954). This increase is blocked by hypophysectomy. Since serotonin is present in relatively high concentration in the hypothalamus, it has been suggested that it may be the physiological mediator for initiating ACTH secretion from the hypophysis (*Way & van Peenan* 1956).

In the present experiments, there was no change in the adrenocortical response to administered ACTH after LSD administration, and the normal response to laparotomy indicates that no inhibition of stress-induced secretion of endogenous ACTH occurred. Similar findings have been reported by *Nadel et al.* (1957), who observed that the injection of 50 μg of LSD in guinea pigs caused no increase in urinary 17-hydroxycorticoid excretion, and no change in the usual rise produced by ACTH administration.

The present results might be interpreted as evidence against a pituitary-stimulating role for hypothalamic serotonin. However, there is considerable debate about whether or not LSD is an antagonist to serotonin in other than certain selected instances (*Rothlin* 1957). In this regard, it is particularly interesting that *Milkovic & Supek* (1956) have reported that LSD fails to block the adrenal cortex stimulating effect of administered serotonin in rats. Conse-

quently, the only conclusion that can be drawn at present is that LSD does not affect adrenal responsiveness to ACTH or sensitivity of the pituitary-adrenal axis to stress.

LSD causes symptoms suggestive of adrenergic discharge in man (*Rothlin* 1957; *Graham & Khalide* 1954; *Rothlin et al.* 1956). *Lidell & Weil-Malherbe* (1953) reported an increase in »adrenaline« in the peripheral plasma of mental patients following LSD administration. The method used did not permit the differentiation between epinephrine and norepinephrine. Others could not confirm this rise (*Manger et al.* 1957) although *Elmadjian et al.* (1958) reported increased catechol secretion in the urine of LSD-treated non-psychotic patients. Changes in catechol amine levels in peripheral plasma and urine of unanaesthetized humans following LSD administration may be secondary to psychic phenomena.

In the present experiments, the epinephrine and norepinephrine secretion rates after LSD and saline administration are all in the range of previously reported resting normal values in the dog (*Goldfien & Ganong* 1959). The rise in epinephrine secretion following the stress of laparotomy seven hours after cannulation in both the LSD-treated and control dogs is somewhat less than that observed after cannulation of previously unstressed dogs under pentobarbital anaesthesia (*Wise et al.* 1960), but the number of determinations is too small to determine if this difference is significant.

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REFERENCES

Bergen J. R. & Beisaw N. E.: Fed. Proc. *15* (1956) 15.
Elmadjian F., Hope J. M. & Lamson E. T.: Recent Progr. Hormone Res. *14* (1958) 513.
Erspamer V.: Pharmacol. Rev. *6* (1954) 425.
Ganong W. F. In: Gorbman A., Ed. Comparative Endocrinology, New York (1959) 187.
Goldfien A. & Ganong W. F.: Fed. Proc. *18* (1959) 54.
Graham J. D. P. & Khalide A. I.: Faculty of Med., Baghdad, Iraq, *18* (1954) 1.
Hoagland H., Rinkel M. & Hyde R. W.: A. M. A. Arch. Neurol. and Psych. *73* (1955) 100.
Hume D. M. & Nelson D. H.: Surgical Form, Am. College of Surgeons (1954) 568, W. B. Saunders and Co. (1955).
Lidell D. W. & Weil-Malherbe H.: J. Neurol., Neurosurg. and Psychiatry *16* (1953) 7.
Lingjærde P. & Skaug O. E.: J. nerv. ment. Dis. *124* (1956) 578.
Milkovic S. & Supek Z.: Arch. exp. Path. Pharmakol. *228* (1956) 146.

Nadel E., Burstein S. & Hoagland H.: Amer. J. Physiol. *189* (1957) 73.
Nelson D. H., Egdahl R. H. & Hume D. M.: Endocrinology *58* (1956) 309.
Rinkel M., Hyde R. W., Solomon H. C. & Hoagland H.: Amer. J. Psychiat. *11* (1955) 881.
Rothlin E.: J. Pharmacy and Pharmacol. *9* (1957) 569.
Rothlin E., Cerletti A., Konzeff H., Schlach W. R. & Taeschler M.: Experientia (Basel) *12* (1956) 154.
Silber R. H. & Porter C. C.: J. biol. Chem. *210* (1954) 923.
Way E. L. & van Peenen P. F. D.: Abstracts, 20th International Physiological Congress (1956) 949.
Wise B. L., Goldfien A. & Ganong W. F.: Acta neuroveg. 22 (1960) 1.

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