

EFFECT OF LYSERGIC ACID DIETHYLAMIDE (LSD)
ON MONOAMINE CONTENT IN SOME NUCLEI
OF THE MESENCEPHALON AND HYPOTHALAMUS

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A definite increase in the content of catecholamines was constantly observed in the mesencephalic reticular formation at the level of the caudal two-thirds of the interpeduncular nucleus, in the substantia nigra, in the zone above the interpeduncular nucleus at the level of its middle third, and in an area situated laterally to the interpeduncular nucleus at the level of its cranial third, in rats 15 and 60 min after injection of lysergic acid diethylamide (LSD) in doses of 20-30 mg/kg and 19 h after injection of LSD in a dose of 0.2-1.2 mg/kg body weight. A decrease in the concentration of catecholamines was observed in the paraventricular, supra-optic, and dorsomedial nuclei of the hypothalamus 60 min after injection of LSD in a dose of 20 mg/kg.

Despite extensive biochemical data concerning the effect of LSD on the content of monoamines in whole brain homogenates [1, 2, 10, 13], the character of its action on metabolism of the biogenic amines in the central nervous system and, in particular, its local effect on function of the monoamine systems of the brain still remain unexplained.

Since the highest concentration of monoamines is found in the mesencephalon and hypothalamus [3-5, 8, 11, 13], these parts of the brain were chosen as objects for a histochemical investigation.

EXPERIMENTAL METHOD AND RESULTS

The concentration of monoamines was determined by the fluorescence method of Hillarp, Falck, and co-workers [6, 7, 9] in V. A. Govyrin's modification. Altogether 53 experiments were carried out on male albino rats weighing 200-250 g. LSD was injected intravenously or intraperitoneally in doses of between 0.12 and 30 mg/kg. Control animals received injections of physiological saline. The animals were decapitated 15-45 min, 1-4 h, and 19 h after injection of LSD.

Intravenous injection of LSD in doses of 20 or 30 mg/kg gave rise to strong motor excitation immediately after injection of the compound. They began to crawl around the cage rapidly, with their body tense, their hair stood on end, and the rats made rapid sniffing movements and secreted saliva. A definite increase in the concentration of catecholamines in the cell cytoplasm (Fig. 1 a-d) was observed in the mesencephalic reticular formation at the level of the caudal two-thirds of the interpeduncular nucleus (Fig. 2 d), the substantia nigra, the zone above the interpeduncular nucleus at the level of its middle third, and in an area situated laterally to the interpeduncular nucleus at the level of its cranial third. In sections through these parts of the brain of the experimental animals, small multipolar cells with bright green fluorescence in the cytoplasm (the nucleus did not fluoresce) were clearly distinguishable, whereas in the same parts of the brain of the control animals a diffuse fluorescence was observed and individual cells could be made

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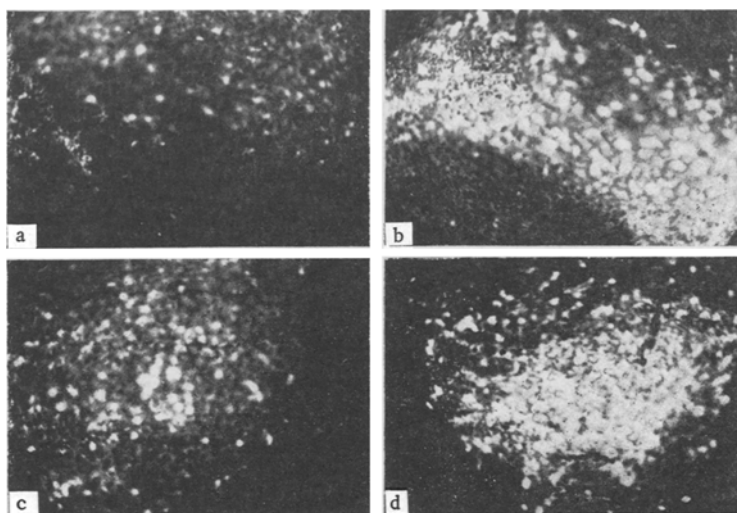


Fig. 1. Increase in concentration of catecholamines in mesencephalon after injection of LSD: a, b) collection of cells in an area of mesencephalon located above the interpeduncular nucleus at the level of its middle third: a) control; b) 19 h after injection of 0.4 mg/kg LSD; c, d) collection of cells in part of mesencephalon located laterally to interpeduncular nucleus at level of its cranial third; c) control; d) 19 h after injection of 0.2 mg/kg LSD, 80 \times .

out only with difficulty or not at all. In the region of the substantia grisea pars ventralis, in the caudal part of the mesencephalon, in 5 of 8 experiments an increase in the concentration of monoamines was observed, in 2 experiments the concentration was reduced, and in 1 experiment it was unchanged. In the dorsal and medial nuclei of the raphe some increase in the concentration of monoamines in the cell bodies was observed after injection of LSD (Fig. 2 a, b). Fluorescence in these nuclei was yellowish in color.

According to data in the literature [7], serotonin is found in the dorsal and medial nucleus of the raphe. Comparison of these facts suggests that LSD influences the serotonin concentration in these nuclei of the mesencephalon.

Green fluorescence only in synaptic endings with varicosities was observed in the hypothalamus of both control and experimental animals.

Some decrease in fluorescence in the paraventricular nucleus was observed in three experiments 15 min after injection of 20–30 mg/kg LSD, an increase was found in two cases, and no change in fluorescence in one experiment. In the supraoptic nucleus a decrease in the concentration of monoamines was found in one experiment, an increase in two, and no change in one of the four experiments. In the dorso-medial nucleus the concentration of monoamines was reduced in two experiments, unchanged in one, and increased in four of seven experiments.

A decrease in the concentration of catecholamines in these parts of the hypothalamus was observed in all three experiments 1 h after injection of the same dose of LSD (20 mg/kg).

Following intravenous or intraperitoneal injection of LSD in doses of 0.12–1.2 mg/kg into rats, weaker motor excitation was observed. The behavioral response of the animals started after 2–3 min. The rats pressed their whole body against the cage floor and started to crawl, sometimes slowly and unsteadily, but occasionally rapidly and suddenly around the perimeter of the cage. They constantly made sniffing movements, breathed rapidly, and their hair was untidy. The rats behaved as if they were looking for something. After this period of motor excitation, which lasted for 45–60 min, the animals gradually became quiet. Sometimes defecation and micturition occurred. The eyes of some animals were widely opened, while those of others, on the contrary, were almost closed.

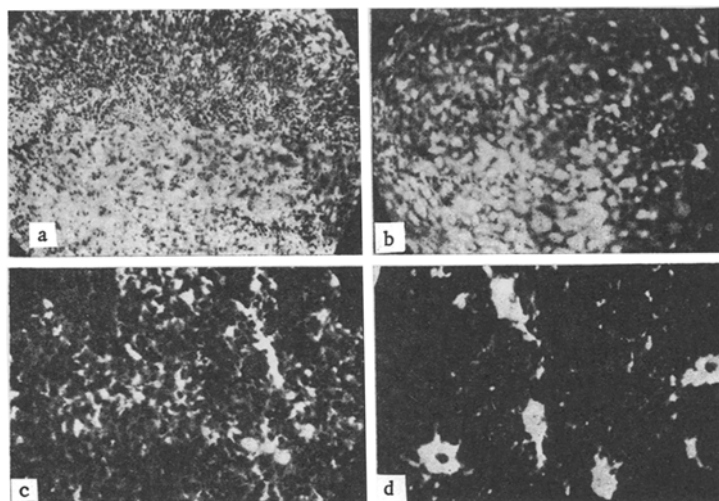


Fig. 2. Appearance of fluorescent nerve cells in mesencephalon of experimental rats after injection of LSD: a, b) dorsal nucleus of raphe: a) control; b) 19 h after injection of 0.4 mg/kg LSD (80 \times); c, d) appearance of brightly fluorescent nerve cells in mesencephalic reticular formation at level of cranial two-thirds of interpeduncular nucleus: c) control; d) 1 h after injection of LSD in dose of 20 mg/kg (320 \times).

After injection of similar doses of LSD, 3 of 53 rats developed motor inhibition. The animals sat on their hind limbs, stretched upward with their whole body, and stood in this position for 10–15 min. Then, while remaining on the spot, they began to move the front part of the trunk very lethargically.

The same general picture of change in the concentration of monoamines as 15 and 60 min after injection of 20–30 mg/kg LSD was observed in the substantia grisea pars ventralis, the dorsal and medial nucleus of the raphe, mesencephalic reticular formation, substantia nigra, in the region above the interpeduncular nucleus, and in the zone located laterally to this nucleus 19 h after injection of 0.2–1.2 mg/kg LSD. However, 20–45 min and 1–4 h after injection of corresponding doses (0.12–1 mg/kg) LSD no changes were found in the concentration of monoamines in the same divisions of the brain.

Some increase in the concentration of catecholamines was observed in the region of the dorso-medial nucleus of the hypothalamus 19 h after injection of 0.4 mg/kg LSD.

These results confirm those obtained by other workers who found that LSD acts upon metabolism of the biogenic amines in the brain [1, 2, 10, 12]. The present results indirectly agree with those obtained by Aleksandrova and Spivakova [2], who report that small doses (0.12–1.2 mg/kg) LSD do not affect the concentration of catecholamines in the brain for comparatively short periods of time (20 min–4 h). On the other hand, the facts obtained contradict the observations of Freedman et al [10, 12] that LSD, in a dose of 0.5–1.3 mg/kg, acts upon the concentration of serotonin in the brain during the first 2 h.

The disagreement between the results of the present experiments and those obtained by Freedman et al. can evidently be attributed to the fact that these workers carried out their experiments by biochemical methods on whole brain homogenates, whereas in the present experiments a histochemical fluorescence method was used, so that local changes in the concentration of monoamines in individual parts of the brain arising through the influence of LSD could be demonstrated.

The present findings definitely show that the psychotomimetic LSD has a definite action on metabolism of the system of biogenic amines in the brain. Under the influence of LSD, functions of the adrenergic structures of the central nervous system show changes to begin with. However, as the present experiments showed, the action of LSD on the neurochemical mechanisms of the brain is highly selective and local and is strictly confined to particular structures of the central nervous system.

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