

The Effect of LSD-25 upon the Cerebral Blood Flow and EEG in Cats

The object of the present study was to determine whether LSD-25 (*d*-lysergic acid diethylamide¹) has any effects upon the cerebral blood flow, the EEG and the blood pressure in anaesthetized and non-anaesthetized (*encéphale isolé*) cats. In recent experimental studies², a sympathomimetic action of LSD-25 in man and experimental animals has been reported. PURPURA³ has analyzed the effects of LSD-25 upon cortical electrical activity. Recently, SOKOLOFF *et al.*⁴ found no changes from LSD-25 in cerebral blood flow, vascular resistance, oxygen consumption, glucose utilization or respiratory quotient in man (normals and schizophrenics). The present experiments have been performed with the method of INGVAR and SÖDERBERG⁵ which provides a continuous registration of the cerebral blood flow with a high degree of accuracy.

In cats under pentothal or of the *encéphale isolé*-type, the venous outflow from the cannulated superior sagittal sinus was continuously measured with an electrical drop counter. Anastomoses between diploic veins and the

sinus were interrupted by a longitudinal craniotomy. The bony defect was filled with dental acrylate cement. EEG was recorded from rostral and parietal parts of the cortex.

Injected intravenously, LSD-25 in doses of up to 10 µg/kg had no effects upon the functions studied. In larger doses up to 100 µg/kg, however, a small transient cerebral vasoconstriction was observed which coincided with a transient 'activation' of the EEG. Sometimes a small cutaneous vasoconstriction was also noted⁶.

Injections into the carotid artery of LSD-25 were also carried out in doses of up to 50 µg/kg. It was then observed that the EEG effects were very pronounced in the homolateral hemisphere. Figure 1 shows a successful example in which 100 µg of LSD-25 were injected into the right carotid artery (*encéphale isolé*-preparation). There was an immediate transient effect of the 'activation' type in both leads from the right hemisphere which, however, was soon followed by a general reduction of the amplitude, an increase in the numbers of spindles and – bilaterally – a generalized decrease in frequency. In about 4 min, the EEG changes had almost disappeared, but a right-sided reduction of the amplitude was still retained.

The flow record shows an immediate vasodilatation followed by a long period during which the flow was practically unchanged in spite of the fact that the blood pressure gradually increased about 30 mm Hg in 5 min. This is interpreted as due to a vasoconstriction in the cerebral vessels. A long-lasting increase of the cerebral vascular resistance was, in fact, the most characteristic effect of LSD-25 seen in the experiments.

In Figure 2 (*encéphale isolé*) another example is given of the effects of 100 µg LSD-25 into the left carotid

¹ W. A. STOLL and A. HOFMANN, *Helv. chim. Acta* 26, 944 (1943). – W. A. STOLL, *Arch. Neurol. Psychiat.* 60, 279 (1947). – LSD-25 was kindly provided by Sandoz A.G., Basel.

² E. ROTHLIN, A. CERLETTI, H. KONZETT, W. R. SCHALCH, and M. TAESCHLER, *Exper.* 12, 154 (1956).

³ D. P. PURPURA, *Arch. Neurol. Psychiat.* 75, 122 (1956); 75, 132 (1956).

⁴ L. SOKOLOFF, S. PERLIN, C. KORNETSKY, and S. S. KETY, *Fed. Proc.* 15, 174 (1956).

⁵ D. H. INGVAR and U. SÖDERBERG, *Nature* 177, 339 (1956); *EEG Clin. Neurophysiol.* 8, 403 (1956); to be published.

⁶ Cf. A. HORITA and J. M. DILLE, *Science* 120, 1100 (1954).

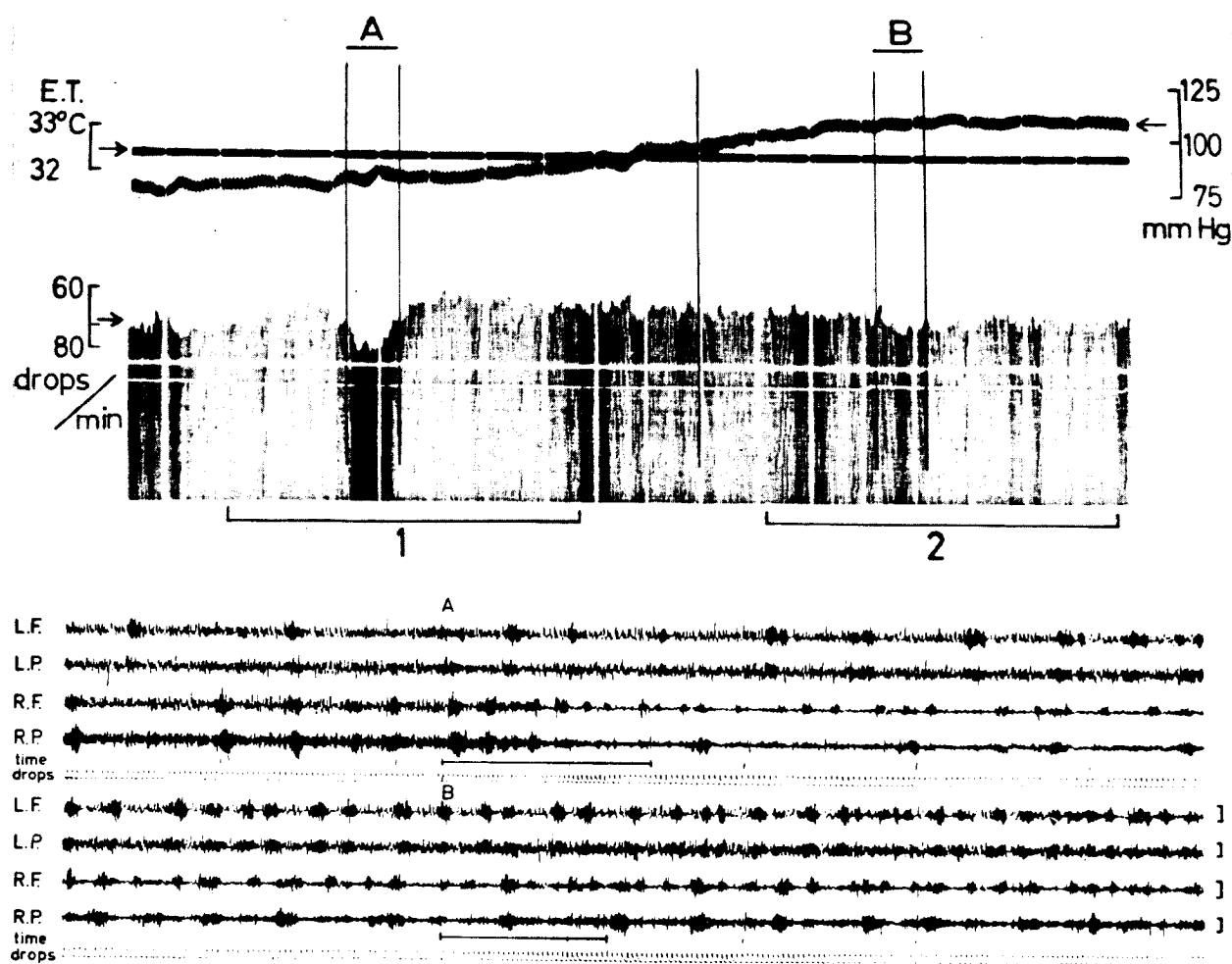


Fig. 1.—Cat, *encéphale isolé*-preparation. *Upper diagram*: Records of ear temperature, blood pressure and cerebral blood flow. Interruptions of diagram every 30 s. Height of vertical lines in flow record is proportional to time interval between blood drops from the cannulated superior sagittal sinus. Thus, a curve joining upper ends of the vertical lines demonstrates variations in cerebral blood flow. *Lower diagram*: Bipolar EEG leads on left frontal (L.F.), left parietal (L.P.), right frontal (R.F.) and right parietal (R.P.) parts of the cortex. EEG samples from p riods marked 1 and 2 in upper diagram. *A*: Injection into right carotid artery of 100 μ g of LSD-25 in 1 ml solution. Note initial transient vasodilatation followed by a period with increasing blood pressure with almost constant cerebral blood flow, indicating vasoconstriction. EEG records demonstrate initial unilateral effects with depression. In sample 2 bilateral EEG effects with increase in number of spindles. *B*: Control injection into carotid artery of 1 ml Ringer solution.

artery. There was a marked ipsilateral activation period in the EEG while the spindle pattern of the opposite hemisphere remained almost uninfluenced. In this case there were no significant changes in the cerebral blood flow.

In deeply anaesthetized preparations LSD-25 did not change the EEG or the cerebral blood flow even in doses of up to 100 μ g/kg given intravenously or into the carotid artery.

The present results have confirmed the findings of SOKOLOFF *et al.*⁴ that doses comparable to those with clinical effects (4 μ g/kg body weight) have no observable effects upon the EEG. Larger doses were, however, found in the present investigation to exert an evident effect upon the cerebral blood flow as well as upon the EEG and systemic circulation. From the results obtained after injection into the carotid artery, it may be reasonable to assume that an important part of the action of LSD-25 is exerted directly upon the cortex, since a brain

stem action would have given bilateral effects⁷. MORUZZI and MAGOUN⁸, however, observed that unilateral electrical stimulation of the reticular activating system of the brain stem may sometimes give desynchronization in the homolateral hemisphere only.

The EEG effects found are in general agreement with the electrophysiological findings of PURPURA³, who demonstrated a facilitatory action of smaller doses and a depressant action of larger doses upon certain central synaptic events.

D. H. INGVAR and U. SÖDERBERG

Nobel Institute for Neurophysiology, Karolinska Institutet, Stockholm, Sweden, August 13, 1956.

⁷ Cf. K. SHIMIZU, S. REFSUM, and F. A. GIBBS, *EEG Clin. Neurophysiol.* **4**, 141 (1952).

⁸ G. MORUZZI and H. W. MAGOUN, *EEG Clin. Neurophysiol.* **1**, 455 (1949).

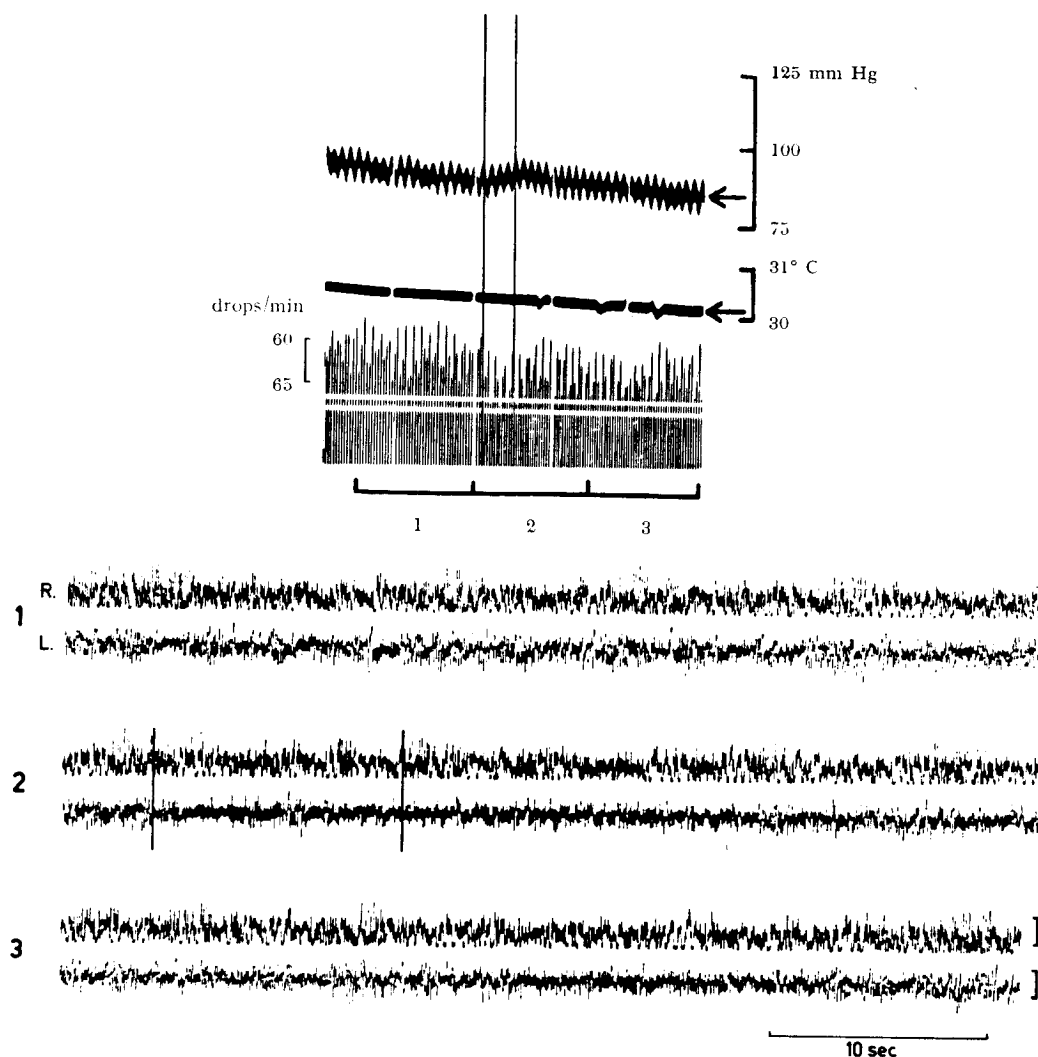


Fig. 2.—Cat, *encéphale isolé* preparation. Upper diagram: Blood pressure, ear skin temperature and cerebral blood flow (Cf. Fig. 1). Lower diagram: EEG tracings from right (R) and left (L) cruciate region during periods marked 1 to 3 below upper diagram. Between two vertical lines injection of 40 μ g/kg of LSD-25 into the left carotid artery. Note activation pattern in EEG-record from left hemisphere.

Zusammenfassung

Es wurde gezeigt, dass LSD-25 (*d*-Lysergsäure-diäthylamid) in Dosen von 30 bis 100 γ /kg Körpergewicht bei nichtnarkotisierten Katzen (*encéphale isolé*) meistens eine Erhöhung des zerebralen Gefäßwiderstandes her-

beiführte. In die Carotis injiziert, gab LSD-25 in denselben Dosen nach vorübergehender, halbseitiger Aktivierung eine Depression des Elektroenzephalogrammes. Kleinere Dosen gaben im EEG eine Aktivierung oder waren ohne Wirkung.