Complete text

*VI LSD No. 262 (§102a) M 500 metabolism

ROTHLIN, E. (Basle)

Metabolism of lysergic acid diethylamide.

Nature 178, 1400 (1956).

In a communication on lysergic acid diethylamide, Axelrod, Brady, Witkop and Evarts[1] state: "Although the hallucinogenic agent, lysergic acid diethylamide, has been the subject of numerous investigations, little is known about its biological fate". However, a number of facts, not mentioned in this communication, about the destruction, distribution and excretion of this compound have recently been published which show that we are not quite as ignorant about the biological fate of this compound as one might infer from this statement.

Lysergic acid diethylamide is neither bound nor destroyed in blood, because, when incubated with blood (rat) at 38° C. for 6 hr. and then assayed for its activity a 100 per cent recovery is obtained. The result is different when this diethylamide is added to homogenates of rat organs. In these, the activity of lysergic acid diethylamide decreases within a few minutes, but there is no, or only a little, further decrease in activity during the following hours and the same results are obtained whether incubation is at 38° C. or at 3° C. The activity of this diethylamide in the incubates has been assayed on the rat uterus by its inhibiting effect on the 5-hydroxytryptamine contraction. With liver and muscle homogenate the activity of the diethylamide became reduced within a few minutes to nearly 50 per cent; but scarcely any further reduction occurred during the next 17 hr. The lysergic acid diethylamide activity of brain homogenates was reduced to 42 per cent after 10 min., and to 21 per cent after 17 hr. These experiments do not differentiate between loss of activity due to binding of this diethylamide to some tissue constituent, and transformation into an inactive compound. The finding of identical results at 3° C. and 38° C., however, speaks against a metabolic transformation of lysergic acid diethylamide in the homogenates[2].

The distribution of lysergic acid diethylamide in blood and tissue at various times after its intravenous injection into mice or rats has been studied by either estimating the diethylamide biologically[2], or by injecting the diethylamide labelled with carbon-14 and determining it chemico-physically[3,4]. There was good general agreement between the results obtained with the two methods. The half-time value reached in blood was 7 min. in the experiments with the labelled diethylamide and 37 min. in those in which diethylamide was assayed biologically. Most of the organs reached the highest level of lysergic acid diethylamide after 10–15 min. and then lost it gradually in the course of the next few hours. The highest concentration was found in the liver after 30 min., when it was about six times greater than in the blood. The order of decreasing concentration

of lysergic acid diethylamide in other organs was: kidney, adrenals, lung, spleen, pancreas, large intestine, heart, skeletal muscle, skin, brain. The concentration in the brain was at all times lower than in the blood.

In the experiments of Boyd *et al.*[3] with labelled diethylamide, 7–8 per cent of the total activity was excreted within 12 hr., about half of this in the expired air, the rest in the urine and fæces, but 70 per cent was found in the intestinal contents. Stoll *et al.*[4] found 50 per cent of the injected dose in the intestinal contents within two hours after the injection.

There is no doubt that lysergic acid diethylamide or its metabolites are excreted in the bile. In experiments in which labelled diethylamide was injected into rats with bile fistulæ, Stoll *et al.* found that the bile contained within 2 hr. 70 per cent of the total radioactivity. The greater part of lysergic acid diethylamide undergoes chemical alteration because the excreted compounds or metabolites, in contrast to the diethylamide, were water-soluble. Paper chromatography revealed that the bile contained three radioactive compounds with the respective R_F values of 0, 0·13, 0·18. These compounds have not yet been identified chemically or biologically. The last two compounds give the Van Urk colour reaction and the blue fluorescence, characteristic for derivatives of lysergic acid, but neither of them is the 2-oxy-lysergic acid diethylamide, a compound obtained by Axelrod *et al.*, with *in vitro* "enzyme systems present in mammalian liver microsomes when supplemented with oxygen and a reduced triphosphopyridine nucleotide generating system". The problem of whether the third metabolite found in bile, which no longer gives the Van Urk colour reaction, is identical with 2-oxy-lysergic acid diethylamide has still to be examined.

E. ROTHLIN

Sonnenweg 6,
Basle.
Oct. 25.

[1] Axelrod, J., Brady, R. O., Witkop, B., and Evarts, E. V., *Nature*, **178**, 143 (1956).
[2] Lanz, U., Cerletti, A., and Rothlin, E., *Helv. Physiol. Acta*, **13**, 207 (1955).
[3] Boyd, E. S., Rothlin, E., Bonner, J. F., Slater, J. H., and Hodge, H. C., *J. Pharmacol.*, **113**, 6 (1955).
[4] Stoll, A., Rothlin, E., Rutschmann, J., and Schalch, W. A., *Experientia*, **11**, 396 (1955).

(Schicksal von LSD im Organismus)

AXELROD et al. (LSD Nr.195/Gy, Rapport 69 II/8) berichtete, dass über das Schicksal des LSD im Körper wenig bekannt sei. Die vorliegende Arbeit gibt eine Uebersicht über Abbau und Ausscheidung von LSD [cf. BOYD et al., LSD Nr.73, Rapport 40/20; BOYD et al., LSD Nr.192/(LAE), Rapport 68 II/9; BOYD, LSD Nr.192a, Rapport 75 II/4; LANZ et al., LSD Nr.112, Rapport 51 II/8; STOLL et al., LSD Nr.126, Rapport 54 II/8].

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