A New Device for Measuring Spontaneous Motor Activity — Effects of Lysergic Acid Diethylamide in Rats

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Abstract. By means of a new automatic apparatus the influence of lysergic acid diethylamide (LSD) on spontaneous motor activity (SMA) was investigated in rats. Both the horizontal and vertical component of SMA were registered simultaneously at various time intervals after i.p. administration of the drug. A biphasic effect of LSD on both parameters was observed—SMA was stimulated in the first phase, while an inhibitory effect appeared with the increasing interval from the drug administration. The horizontal component was found to be more sensitive to the stimulatory effect while inhibition was more marked in the vertical activity.

Key words: Automatic Device — Spontaneous Motor Activity — Lysergic Acid Diethylamide.

Introduction

Considerable attention is paid to spontaneous motor activity (SMA) investigation in the study of higher nervous activity in animals. SMA as an elementary component of animal behavior is being investigated in a number of laboratories using many different devices. Apart from subjective evaluations objective, and as far as possible automatic and quantitative records of the motility of experimental animals are also being made. With indirect methods of SMA registration such as treadwheels (Wiedemeijer and van Eick, 1960), jiggle cages (Kosman, 1965) or tilt cages (Göswald *et al.*, 1966) a feed-back effect on motor activity could not be excluded. By means of direct methods of SMA recording, a large number make use of photocells (Waltzman *et al.*, 1966; Davis *et al.*, 1967), capacitance sensing devices (McClelland, 1965; Holland *et al.*, 1966), contact systems (Knoll and Vajnovszky, 1961), magnetic pick-up (Mitchell, 1959), loudspeaker (Word and Stern, 1958), piezoeffect (Alvarez-O'Burke and Redetzki, 1963) or electromagnetic

transducers (Zeier and Tschanen, 1968). Nevertheless, the results obtained by the above methods are either difficult to quantify or only one component of SMA is followed. We have tried to obtain automatic registration of both horizontal (HA) and vertical activity (VA) simultaneously in the same exerimental box, and the device used is described in this communication.

The effects of lysergic acid diethylamide (LSD) were studied using this apparatus. Inhibition of SMA has been found by several authors (Taeschler *et al.*, 1960; Fraňková, 1963), but a stimulatory effect of LSD has also been described (Dandiya *et al.*, 1969a, b). Some other authors referred to a biphasic effect of this drug with regard to the dose on conditioned behavior (Cook and Weidley, 1951), on operant behavior (Jarrard, 1963), on the time after drug administration (Winter and Flataker, 1956) and on observations of gross behavior in rats (Hamilton, 1960). We have tried to verify the effects of LSD on both the horizontal and vertical component of SMA in our automatic apparatus. In our experiments only males were used because, as shown previously (Kabeš, 1969), there is no qualitative intersexual difference in spontaneous behavior in rats under LSD influence.

Materials and Methods

Experimental Animals

120 male albino rats of a Wistar-derived strain were used. They weighed 150—170 g at the start of the present work and had not previously been used for experimental purposes. They were housed in groups of four in plexiglass cages and had free access to food and water except during experimental sessions. The animals were kept in a room with relatively constant humidity and temperature (22 $\pm$ 2°C) and adapted to these conditions for two weeks prior to experimentation.

Apparatus

A new experimental device for recording SMA was used, which allows simultaneous automatic registration of both horizontal and vertical components of SMA. The experimental box is constructed of 5 mm thick plastic with interior dimensions of $60 \times 36 \times 28$ cm (Fig. 1). Only the front wall is transparent and observation of tested Ss is possible. The plastic cover of the box is coupled with an aluminium plate. The floor is made from cuprextite, which is a plastic plate coated by a copper membrane on the lower side where grooves of about 1 mm are cut out (Fig. 2a). In this way 15 copper squares, 6×6 cm each, 6 cm apart are isolated. The animal is allowed to walk on the plastic side of the floor and all crossings of the invisible fields are summed to express the

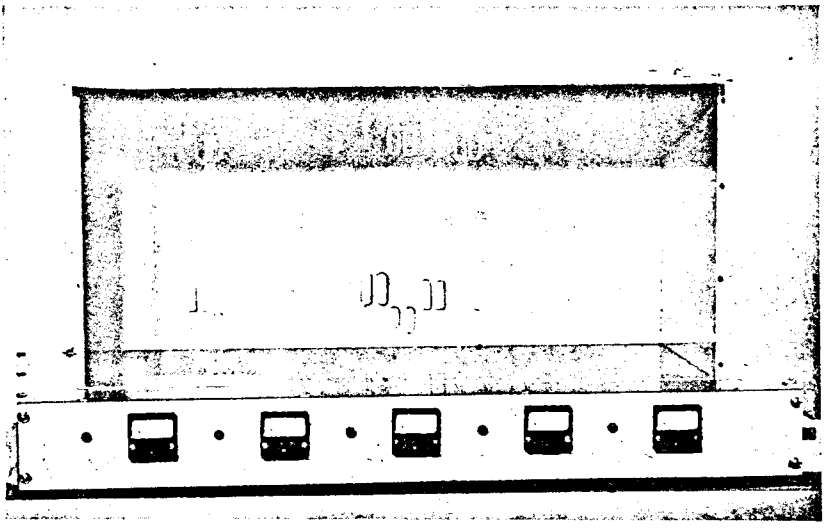

Fig. 1. The experimental box for an automatic evaluation of horizontal and vertical activity in small laboratory animals

horizontal activity score. There are five different types of squares (A, B, C, D, E, see Fig. 2b) and thus five tuned circuits, which are equipped by crystals with different frequencies, 50 kc/sec apart (800 to 100 Kc/sec, Fig. 3). No square adjoins another one of the same type. Thus the animal leaving one field has to enter one of a different type. Squares of one type make up a condenser with their environment. Part of the respective tuned circuit is put of tune by the presence of an animal's body.

An electrically independent principle is used for the VA registration. A widespread classical capacity circuit was used, where the two metal plates of the floor and cover of the box form a condenser (Vondráček *et al.*, 1968). An rearing above an adjustable level changes the capacity and is automatically registered. All rearings are summed successively as a VA score on digital counters. The record of both HA and VA scores is mediated by the pulse counter with the time record on a teletype or a punched tape (Kabeš, 1970). The registration equipment is placed in a separate sound-proof room.

Procedure

Both the horizontal and vertical component of SMA was measured during 10 min sessions with the exception of the group tested 5 min after LSD administration, where each session lasted 5 min only. Ten

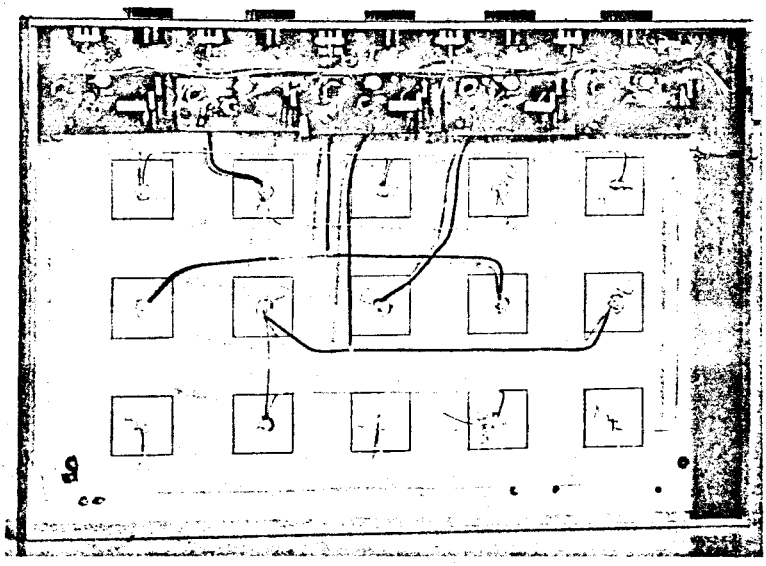

Fig. 2a. A view on the lower side of the floor of the experimental box

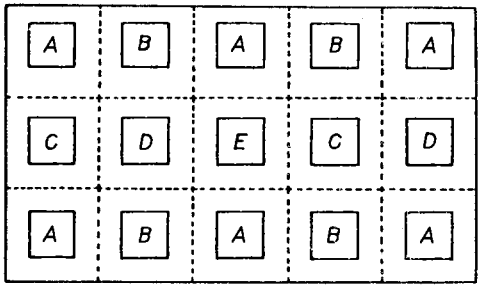

Fig. 2b. Scheme of the floor of the experimental box

consecutive sessions one week apart were performed in all the animals used. After the initial 4 control sessions all the animals were aligned according to their total scores of both HA and VA. The assortment into 15 experimental and 5 control subgroups was made according to this scheme: C_a, D_{1a}, D_{2a}, D_{3a}, C_b, D_{1b}, D_{2b}, D_{3b}, C_c, D_{1c}, D_{2c}, D_{3c}, C_d, D_{1d}, D_{2d}, D_{3d}, C_e, D_{1e}, D_{2e}, D_{3e}; D_{3e} . . . C_a; the sequence of the next 20 Ss being always inverted. In the case of a linear decrease of activity among the ranged animals this procedure was expected to minimize the variability among the subgroups.

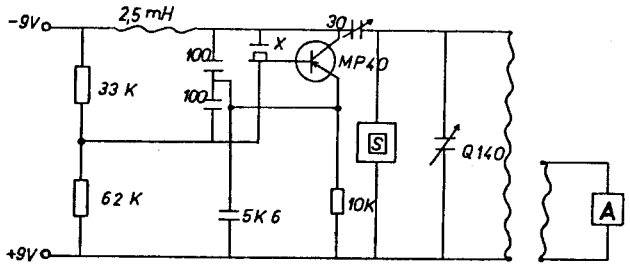

Fig. 3. Tuned circuit diagram. *S* one square of the floor; *X* crystal; *A* amplifier

The influence of 80 (D_1), 200 (D_2) and 500 (D_3) mcg/kg LSD (Lysergamid Spofa) was studied in the next 4 succesive sessions starting 5 (a), 10 (b), 20 (c), 90 (d) and 270 (e) min after intraperitoneal administration. Saline solution (C) was given to the control subgroups. Finally, the last 2 sessions were performed again under control conditions in all animals. By this design drug effect can be evaluated against parallel controls in the experimental sessions and against their own control results from the sessions before and after LSD influence. The first 2 sessions are usually out of the linear trend of habituation (Kabeš, unpublished results) and were eliminated from statistical analysis. Thus a symmetrical model was obtained: 2 control, 4 experimental and again 2 control sessions, where a linear effect of the repeated exposures to the experimental environment was established.

Statistical Analysis

On the basis of our previous results we assume that HA and VA can be modelled by a stochastic Poisson process. Activity scores "x" (i.e. the number of rearings—VA, or the squares which were crossed—HA, during each session) are then random variables with a Poisson distribution. To stabilize the variance and get approximately normal variables we transformed the activity scores using the well known square root transformation:

$$y = \sqrt{x + 3/8}\,.$$

The analysis of the results was performed by applying the following regression model to the transformed data "y" (for HA and VA separately):

$$y_{ijt} = \mu_{ij} + \delta_t(\gamma + \varrho z_i') + \beta_t + z_{ijt}$$

where $i = 1, \ldots, 4$ for groups of Ss, $j = 1, \ldots, 6$ for S in the group, $t = 1, \ldots, 8$ for sequence number of the session, z_{ijt} = independent and normally distributed variables with zero mean and constant vari-

ance, $\delta_t = 1$ for the experimental sessions, $\delta_t = 0$ for the control sessions, β = regression coefficient of the activity trend in repeated sessions (habituation coefficient), μ_{ij} = average activity of an individual rat, z_i' = dose logarithm, $\gamma + \varrho z_i'$ = changes of activity after drug administration (linearly dependent on the log-dose). All the parameters were estimated by the maximum likelihood method, the residual variance was calculated and differences from zero of the estimates for the drug effect and effect of habituation were tested.

All calculations were performed on the MINSK 22 computer.

Table 1. *Regression coefficients of the activity trend in repeated sessions (habituation coefficients β and their standard errors)*

Time	HA	VA
5	− 0.003 ± 0.006	− 0.044 ± 0.001*
10	0.034 ± 0.008*	− 0.079 ± 0.002*
20	− 0.005 ± 0.007	− 0.087 ± 0.002*
90	− 0.129 ± 0.008*	− 0.112 ± 0.002*
270	− 0.025 ± 0.006*	− 0.075 ± 0.002*

* Significant at $P < 0.05$.

Table 2. *Effects of LSD treatment on the horizontal and vertical activity (coefficients γ and their standard errors)*

Time	HA	VA
5	1.070 ± 0.56	0.321 ± 0.13*
10	0.289 ± 0.67	0.092 ± 0.17
20	0.306 ± 0.57	− 0.376 ± 0.13*
90	− 0.669 ± 0.66	− 0.368 ± 0.18*
270	− 0.967 ± 0.47*	− 1.197 ± 0.19*

* Significant at $P < 0.05$.

Table 3. *Dependence of the drug effect on the dose used (coefficients ϱ = regression on log-dose and standard errors)*

Time	HA	VA
5	0.349 ± 0,53	− 0.032 ± 0.12
10	0.313 ± 0,65	− 0.058 ± 0.16
20	0.192 ± 0,53	− 0.196 ± 0.12
90	− 0.266 ± 0,62	− 0.213 ± 0.17
270	− 0.151 ± 0,44	0.119 ± 0.18

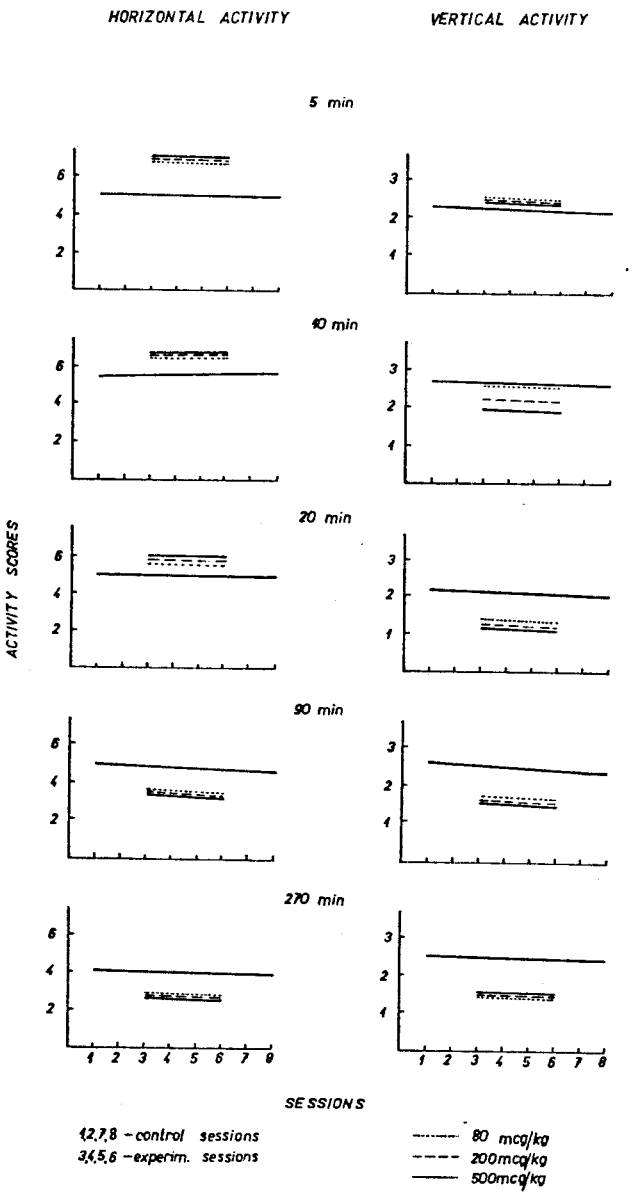

Fig. 4. Changes of horizontal and vertical activity after LSD administration ($\gamma + \varrho \cdot z_i'$)

Results

The influence of repeated exposures to the experimental environment on SMA is shown in Table 1. Habituation coefficients β characterize

linear activity changes in the consecutive sessions. With only one exception (HA, 10 min) there is a decrease of both HA and VA during the experiment, which is obviously due to the phenomenon of habituation.

Drug effect is characterized by the coefficients γ which are given in Table 2. A biphasic effect of LSD was found in both the registered parameters. The initial stimulation of activity is significant in VA only, while the changes in HA are nonsignificant, presumably because of the considerable inter-individual variability in the activity scores. The later decrease in HA and VA after LSD was significant until 270 min after drug administration.

The effect of different doses of LSD was not significant (coefficients ϱ—Table 3). The reason is probably again in the great variability, although some trends may be followed (see discussion). The changes in horizontal and vertical components of SMA at different intervals after the administration of different doses of LSD ($\gamma + \varrho \cdot z_i'$) are graphically expressed in Fig. 4.

Discussion

The apparatus described makes possible a fully automatic registration of horizontal and vertical movements of small laboratory animals. By means of some simple accessories it is possible to record even the qualitative patterns of spontaneous behavior (Kabeš, 1970b). By combining the device with a suitable registration unit the results may be obtained in a quantitative form. The construction is relatively easy and cheap, and servicing is quite simple. In our laboratory the apparatus has been in action for more than two years without any defect.

The results presented were obtained from the initial experiments made on this apparatus. A biphasic effect of LSD on SMA was demonstrated and these results support our previous findings of LSD influence on SMA in circular actographs (Kabeš and Fink, 1969).

The significance of the drug effect is influenced, to a certain extent, by the selection of experimental animals, which was purposely oriented by the effort to obtain a widespread scale of initial activity scores. Experiments performed with a sufficient number of animals have a more general validity. In further experiments drug effects in rats strictly selected according to the initial activity will be examined.

In the first test (beginning 5 min after LSD administration) the duration chosen was only 5 min, because the maximal stimulatory effect of LDS on SMA in circular actographs was observed at this interval (Kabeš and Fink, 1970). In fact, this is the only period in which LSD produced a stimulation of both HA and VA. In the further two tests (beginning 10 and 20 min after LSD administration) there was a difference between the drug effect on the two components of SMA ob-

served. In general, there is a tendency for an indirect dose-dependence of VA during the short stimulatory phase, while for HA the higher the dose the greater the effect, and the stimulation lasts for 30 min. The VA appears more sensitive to the inhibitory influence of LSD, for inhibition appears sooner than in the HA, and following the higher doses even interferes with the initial stimulatory effect. This suggestion is in aggrcement with the conclusions of preliminary experiments (Kabeš, 1969), where a similar character of LSD influence of SMA in rats of both sexes could be followed.

Another observation may also support there results. Dandiya *et al.* (1969b) described a dose-dependent stimulatory effcct on ambulation in rats after doses ranging from 2 to 500 mcg/kg LSD, while rearing exhibited an inverted U type dose-response relationship in Open Field behavior. The drug was administered intraperitoneally 15 min before the tests which lasted 2 min. Probably, in these experiments the inhibitory component of LSD effect on rearing plays a role in higher doses only (regarding a single test interval), while the lower doses have a stimulatory effect. Concerning ambulation, the observation was probably performed during the stimulatory phase, thus the effect could increase when the higher doses were used.

The results also confirm the investigation of Winter and Flataker (1956), who postulate a biphasic effect of 500 mcg/kg LSD on SMA. We observed the rats crawling around on the floor as did there authors. This abnormal behavior may be one of the factors influencing the intensity of the vertical component of SMA, while the stimulation of the HA need not be affected. This phenomenom was not quantified in our experiments and its motivation is still unclear. In a further analysis of behavioral effects of LSD the above mentioned behavior as well as some other qualitative behavioral changes should be paid greater attention. It was shown, for example, that the activity did not increase at the cost of the rest intervals but a corresponding shorthening of cleaning periods occurred (Kabeš, 1970b).

The discrepancies in the described behavioral effects of LSD mentioned seem to be due mainly to different experimental conditions used by different authors. Obviously, the drug effect, being so complicated as can be seen in the case of LSD, should be investigated at different intervals after the administration of several doses and, as far as possible, in more than one experimental situation. Attention should also be paid to qualitative behavioral patterns induced by drug influence.

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References

Alvarez-O'Burke, F., Redetzki, H.: A simple device for the measurement of the spontaneous movements of animals. Arch. int. Pharmacodyn. **142**, 516—521 (1963).

Cook, L., Weidley, E.: Behavioral effects some psychopharmacological agents. Ann N.Y. Acad. Sci. **66**, 740—750 (1957).

Dandiya, P. C., Gupta, B. D., Gupta, M. L.: The effect of central nervous system activating on the open field performacne of rats. Presented on the VIth Int. Congress on Pharmacology, Basel 1969a.

— — — Patni, S. K.: Effects of LSD on open field performance in rats. Psychopharmacologia (Berl.) **15**, 333—340 (1969b).

Davis, W., King, W. T., Babbini, M.: Placebo effect of saline on locomotor activity in several strains of mice. J. Pharmac. Sciences **56**, 1347—1349 (1967).

Fraňková, S.: The influence of benactyzine and LSD on the higher nervous activity in rats. Activ. nerv. sup. (Praha) **3**, 214 (1963).

Gösswald, R., Lettau, E., Mennecken, W.: Automatische Registrierung der Motilität von Mäusen. Arzneimittel-Forsch. **16**, 656—658 (1966).

Hamilton, L. Ch.: Effect of LSD-25 and amphetamin on a running response in the rat. Arch. gen. Psychiat. **2**, 104—109 (1960).

Holland, H. C., Gupta, B. D., Weldon, E.: A note on rearing and an environmental constraint. Activ. nerv. supl (Praha) **8**, 140—144 (1966).

Jarrard, L. E.: Effects of D-lysergic acid diethylamide on operant behavior in the rat. Psychopharmacologia (Berl.) **5**, 39—46 (1963).

Kabeš, J.: Spontaneous motor activity in rats after LSD influence. Československá fyziologie **18**, 312 (1969).

— Alteration of some patterns of spontaneous motor activity in rats after LSD influence. Presented on the 9th Interdisciplinary Conference on the Experimental and Clinical Study of the Higher nervous Functions, Mariánské Lázně 1970a.

— LSD—a study of some qualitative behavioral effects in rats. Collect. Sci. Works PMRI **49**, 157—166 (1970b).

— Fink, Z.: Spontaneous motor activity and acetylcholine brain metabolism in rats after LSD administration. Presented on the VIth International Congress on Pharmacology, Basel 1969.

— — Changes of spontaneous motor activity in an early phase after the administration of lysergic acid diethylamide. Collect. Sci. Works PMRI **49**, 133—144 (1970).

Knoll, J., Vajnovszky, B.: Motimeter, a new sensitive apparatus for the quantitative measurement of hypermotility caused by psychostimulants. Arch. int. Pharmacodyn. **12**, 141—154 (1961).

Kosman, M. E.: The effect of grouping on the rat's response to a psychotomimetic agent. Int. J. Neuropsychiat. **12**, 90—94 (1965).

McClelland, W. J.: An electronic apparatus for recording movement in small animals J. exp. Anal. Behav. **8**, 215 (1965).

Mitchell, W. C.: Differentiation of activity of three mouse strains with magnetic pick-up apparatus. Science **130**, 455 (1959).

Taeschler, M., Weidmann, H., Cerletti, A.: Die Wirkung von LSD auf die Reaktionszeit bei einer bedingten Flutchreaktion und im Analgesis Test. Helv. physiol. pharmacol. Acta **18**, 43—49 (1960).

Vondráček, V., Fink, Z., Kabeš, J.: An automatic equipment for registration and evalution of behavior in laboratory animals. Collect. Sci. Works PMRI **32**, 353—360 (1968).

Watzman, N., Barry, H., Kinnard, W. J., Buckley, J.: Comparison of different photobeam arrangements for measuring spontaneous activity of mice. J. Pharmacol. Sci. 55, 97 (1966).

Wiedemeijer, J. C., Van Eick, A. J.: A simple device to measure the activity of mice. Acta physiol. pharmacol. neerl. 9, 509–513 (1960).

Winter, C. A., Flataker, L.: Effects of lysergic acid diethylamide upon performance of trained rats. Proc. Soc. exp. Biol. (N.Y.) 92, 285–289 (1956).

Word, T., Stern, J. A.: A simple stabilimeter. J. exp. Anal. Behav. 1, 201–203 (1958).

Zeier, H., Tschannen, G.: A new device for measuring general locomotor activity in instrumental conditioning situations. J. exp. Anal. Behav. 11, 63–64 (1968).

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