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Hyperthermic Effects of D-Lysergic Acid Diethylamide (LSD) and its Derivatives in Rabbits and Rats

H. HASHIMOTO (1) (4), M. HAYASHI (1), Y. NAKAHARA (2), T. NIWAGUCHI (2) AND H. ISHII (3)

(1) *Research Institute for Chemobiodynamics and* (3) *Faculty of Pharmaceutical Sciences, Chiba University, Chiba, Japan.*

(2) *National Institute of Police Sciences, Chiyoda-ku, Tokyo, Japan.*

Abstract—Several D-lysergic acid diethylamide (LSD) derivatives including metabolites of LSD in animals liver and Streptomyces such as D-lysergic acid ethyl, 2-hydroxyethylamide (LEO), D-lysergic acid ethylamide (LAE), D-norlysergic acid diethylamide (norLSD) and synthetic N^6-allyl-D-norlysergic acid diethylamide (allyl-norLSD) were studied with regard to their hyperthermic effect in rabbits and rats. In rabbits, the order of the hyperthermic activities was allyl-norLSD > LSD > LEO, LAE, norLSD, and this order was parallel to that of 5-hydroxytryptamine-like activities of these compounds which was previously studied. However, the order was LAE > LSD > norLSD in rats. The hyperthermic effect of LSD in rabbits was attenuated by methysergide, but not by atropine when these drugs were intraventricularly administered. These results suggest the possibility that the metabolites of LSD contribute to the hyperthermic effect of LSD in rats but not in rabbits, and support the idea that 5-HT receptors are involved in the hyperthermia induced by LSD in rabbits.

Introduction

Since Axelrod *et al.* (1) have found 2-oxylysergic acid diethylamide to be a metabolite of D-lysergic acid diethylamide (LSD), several compounds have been reported to be metabolites of LSD (2–4). Recently, D-lysergic acid ethylamide (LAE) and D-norlysergic acid diethylamide (norLSD) also have been demonstrated to be metabolites of LSD in animal liver in vitro (5). In addition,

(4) Present address: Department of Pharmacology, Hamamatsu University School of Medicine, Handa-cho, Hamamatsu, Japan.

D-lysergic acid ethyl, 2'-hydroxyethylamide (LEO) and D-lysergic acid ethyl, vinyl were found to be new metabolites of LSD in Streptomyces by Hayashi *et al.* (6). Previously we have studied the effects of these metabolites as well as N^6-allyl-D-norlysergic acid diethylamide (allyl-norLSD) on 5-hydroxytryptamine receptors in the rat uterus, and suggested that the metabolites of LSD such as LEO, LAE and norLSD had lower 5-HT-like activities than LSD, and that allyl-norLSD had higher 5-HT-like activities than LSD (7, 8). The present investigation was undertaken to study the hyperthermic effects of these compounds in rabbits and rats. The relationship between the hyperthermic activities of these compounds and their 5-HT-like activities is also discussed.

Methods

Albino male rabbits and Wistar male rats were used. The experiments were performed between 11 A.M. and 6 P.M. at a room temperature of 22 to 24° C. Animals were allowed free access to food and water at all times. Rectal temperatures were measured by an electronic thermometer (Nihon Kohden, MGA 111–219), and taken at 15 min to 1 hr intervals for periods of 2 to 5 hr. Drugs were dissolved with pyrogen-free 0.9 % sodium chloride solution.

Rabbits: LSD derivatives were administered via the marginal ear vein or the cerebral ventricles. The hyperthermic effects of the intravenous administration of derivatives were studied with rabbits weighing 1.7 to 2.2 kg. The LSD derivatives were used at a dose of 12.5 μg/kg or 50 μg/kg. 5-hydroxytryptophane (5-HTP) was administered intravenously or intraperitoneally at a dose of 20 mg/kg or 30 mg/kg respectively. Pargyline, 50 mg/kg, was subcutaneously administered 2 hr before the administration of 5-HTP.

The hyperthermic effects of the intraventricular administration of drugs were studied with rabbits weighing 2.6 to 3.2 kg. For the injection of drugs into the cerebral ventricles a polyethylene guide cannula which was cleaned with pyrogen-free water was aseptically implanted under pentobarbitone sodium anaesthesia into the left lateral ventricles according to the following coordinates from the atlas of Sawyer *et al.* (9): A 1.0, L 2.5, H 5.0, and was permanently affixed to the skull by Aron Alpha (Toa Gosei Chem. LTD) and a dental cement. The guide cannula was occluded with a stainless-steel stylet. At least 1 week was allowed for surgical recovery. The guide cannula was washed with pyrogen-free saline the day prior to the injections of drugs. The injections of drugs were made in a volume of 0.05 to 0.1 ml. Methysergide 100 μg, phenoxybenzamine 200 μg or atropine 400μg was injected into the lateral ventricles an hour prior to the injection of LSD, epinephrine or saline. The rise in the rectal temperature was measured 30 min after the administration of the pyretogenic agents or saline. The data were analyzed for statistical significance by the Student's t-test.

Rats: Wistar male rats weighing 250 to 300 g were employed. Drugs were intraperitoneally administered.

Drugs: The following drugs were employed: D-lysergic acid diethylamide tartrate (Sandoz), 5-hydroxy-DL-tryptophane (Nakarai Chem.), pargyline hydrochloride (Nakarai Chem.), l-epinephrine d-bitartrate (Nakarai Chem.), atropine sulfate (Nakarai Chem.), phenoxybenzamine hydrochloride (Nakarai Chem.). The derivatives of LSD such as D-lysergic acid ethylamide tartrate (LAE), D-lysergic acid ethyl, 2′-hydroxyethylamide tartrate (LEO) and N^6-allyl-D-norlysergic acid diethylamide tartrate (allyl-norLSD), were prepared as reported previously (6, 10, 11). The doses of drugs are represented as salts.

Results

1. Effects of intravenous administrations of LSD derivatives in rabbits

LSD, 50 μg/kg, produced a prolonged rise in the rectal temperature within half an hour after the administration, as shown in Fig. 1. LAE, 50 μg/kg, also

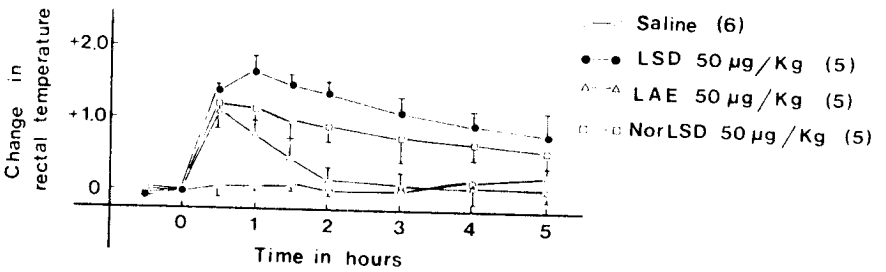

FIG. 1

The hyperthermic effect of intravenous injections of LSD and its metabolites in rabbits. Drugs were injected at zero time. The vertical bars indicate the standard deviations. Numbers in parentheses indicate the numbers of animals used.

showed pyretogenic effects. The maximum rise of the rectal temperature by LAE was observed at half an hour after the administration, and the effect of LAE subsided faster than the effect of LSD. NorLSD, 50 μg/kg, showed remarkable pyretogenic effects and the time course of the effect of norLSD was similar to that of LSD. LSD, 12.5 μg/kg, also showed pyretogenic effects, whereas the same dose of LAE or norLSD showed only slight effects (Table I). The pyretogenic effect of 50 μg/kg LEO was slightly less than that of LSD. A N^6-substituted derivative, allyl-norLSD, 50 μg/kg, showed the most remarkable hyperthermia among the derivatives tested.

2. Effects of intraventricular injections of LSD derivatives in rabbits

As shown in Fig. 2, physiological saline 0.1 ml did not produce any significant

TABLE I

Maximum rise in the rectal temperature by LSD derivatives in rabbits

Compounds	Dose	
	12.5 μg/kg	50 μg/kg
LSD	1.35 ± 0.35 (4)	1.77 ± 0.22 (5)
LEO		1.24 ± 0.21 (5)
LAE	0.50 ± 0.22 (4)	1.16 ± 0.26 (5)
NorLSD	0.58 ± 0.17 (4)	1.20 ± 0.19 (5)
Allyl-norLSD		3.36 ± 0.83 (6)

Values are means ± S.D.
Numbers in parentheses indicate the numbers of animals used.

change in the rectal temperature. The intraventricular injection of LSD, 5 μg, produced marked hyperthermia. The effect of the same dose of LAE or LEO was very small.

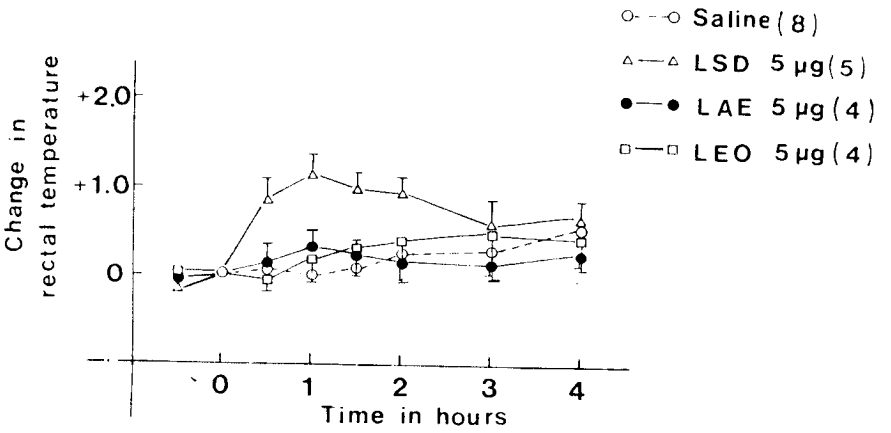

FIG. 2

The effect of intraventricular injections of LSD and its derivatives on the rectal temperature in rabbits. For further details see Fig. 1.

3. Effect of the intravenous or the intraperitoneal injection of 5-HTP in rabbits

5-HTP, 20 mg/kg, did not produce any significant change in the rectal temperature normal rabbits. In rabbits pretreated with pargyline, the i.v. injection of 5-HTP, 20 mg/kg, produced hypothermia in 4 out of 6 animals tested, and in the other 2 animals it produced hyperthermia (Fig. 3A). The effect of i.p. injections of 5-HTP, 30 mg/kg, was tested in rabbits pretreated with pargyline (Fig. 3B). In rabbit A, 5-HTP produced hyperthermia, and in rabbit B it produced initially no change and then hyperthermia. In rabbit C, 5-HTP initially produced hypothermia and then hyperthermia about 3 hr after the 5-HTP injection.

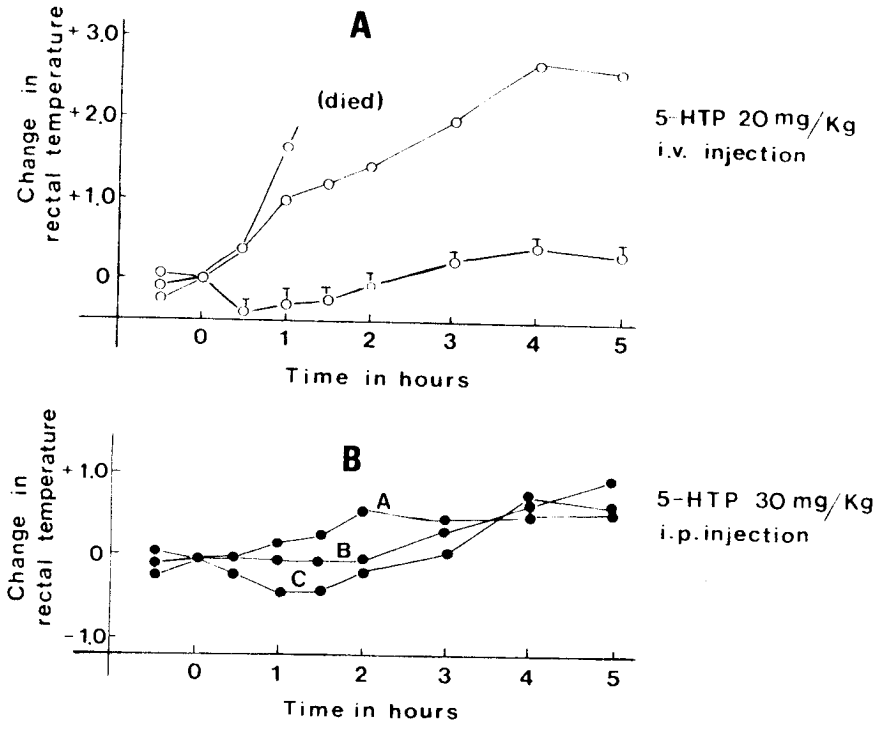

FIG. 3

The effect of 5-HTP on the rectal temperature in rabbits. Pargyline 50 mg/kg was administered 2 hr before the injection of 5-HTP. A: effect of the intravenous injection of 5-HTP 20 mg/kg. B: effect of the intraperitoneal injection of 5-HTP 30 mg/kg. For further details see Fig. 1 and text.

4. Effects of the intraventricular injections of methysergide, phenoxybenzamine and atropine on the hyperthermic effect of LSD in rabbits

Methysergide, 100μg, significantly attenuated the hyperthermic effect of

TABLE II

Effects of the intraventricular injections of phenoxybenzamine, methysergide and atropine on the hyperthermic effect of LSD in rabbits

Drugs	N	Rise in rectal temperature (mean ± S.D.)
Epinephrine 150 μg	4	1.15 ± 0.29
PBA 200 μg + Saline	6	0.15 ± 0.28
PBA 200 μg + Epinephrine 150 μg	5	0.12 ± 0.30**
LSD 5 μg	5	0.88 ± 0.26
PBA 200 μg + LSD 5 μg	6	0.53 ± 0.15*
Methysergide 100 μg + Saline	4	0.05 ± 0.29
Methysergide 100 μg + LSD 5 μg	4	0.33 ± 0.10**
Atropine 400 μg + Saline	3	0.07 ± 0.15
Atropine 400 μg + LSD 5 μg	4	0.78 ± 0.30

PBA: Phenoxybenzamine. — N: number of animals used. — Rises in rectal temperature were measured 30 min after the injection of epinephrine, LSD or saline. — ** $P < 0.01$. — * $P < 0.05$ compared to the response in the absence of phenoxybenzamine or methysergide.

LSD (Table II). Phenoxybenzamine, 200 μg, which completely abolished the hyperthermic effect of epinephrine, 150 μg, significantly attenuated the effect of LSD. Although atropine, 400 μg, alone produced a fall in the rectal temperature of 0.2° C to 1.4° C, it did not attenuate the effect of LSD.

5. Effects of LSD and its derivatives on the rectal temperature in rats

Results are shown in Fig. 4. The intraperitoneal injection of LSD, 1 mg/kg, produced a significant rise in the rectal temperature within 15 min. The same

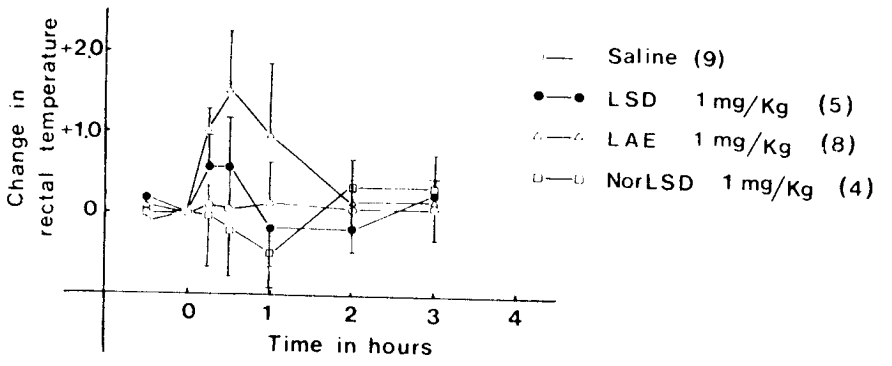

FIG. 4

The effect of intraperitoneal injections of LSD and its metabolites on the rectal temperature in rats. For further details see Fig. 1.

dose of LAE showed the most remarkable pyrotogenic effect. NorLSD, 1 mg/kg, did not produce any pyretogenic action.

Discussion

The present study shows that the metabolites of LSD produced hyperthermic effects in rabbits and rats. In rabbits, 12.5 μg/kg of LSD produced marked hyperthermia, whereas the same dose of LAE or norLSD produced only slight hyperthermia (Table I). In addition, the hyperthermic effect of LAE subsided rather rapidly. Therefore, it is unlikely that the metabolites contribute to the hyperthermic effects of LSD in rabbits. On the other hand, LAE produced a more marked hyperthermia than LSD in rats (Fig. 4), suggesting the possibility that LAE contributes to a certain extent to the hyperthermia induced by LSD in rats.

As shown in Fig. 1 and Table I, when injected intravenously in rabbits, the pyretogenic activity of allyl-norLSD was high, and the activity of LEO, LAE or norLSD was low. Because the hyperthermic activity of LAE or LEO was lower than that of LSD when these drugs were injected intraventricularly (Fig. 2), it is unlikely that these metabolites could not penetrate through the blood-brain barrier resulting in a low hyperthermic activity. Previously we have studied 5-HT-like activities of LSD derivatives in the rat uterus, and found that the order of the 5-HT-like activities was allyl-norLSD > LSD > LAE, LEO, norLSD (7, 8). Therefore, the hyperthermic activities of these compounds in rabbits were parallel to their 5-HT-like activities. These facts support the idea that the hyperthermic actions of LSD and its derivatives are 5-HT-like (12–15). However, 5-HTP produced not only hyperthermia but also hypothermia in rabbits (Fig. 3). Dual effects of 5-HT also have been shown (16, 17). It has been reported that 5-HT- and 5-HTP-induced hyperthermia were inhibited by antiserotonin drugs (12, 16, 17), indicating the involvement of 5-HT receptors in hyperthermia induced by 5-HT and 5-HTP.

Hyperthermia induced by LSD has been reported to be affected by many drugs (12, 18–20). However, it must be considered that those drugs show peripheral effects beside the central effects, when drugs were peripherally administered. In the intraventricular injection study (Table II), the hyperthermic effect of LSD in rabbits was attenuated by methysergide, but not by atropine. It has been shown that the i.v. injection of antiserotonin drugs attenuated hyperthermia induced by LSD (12–14). These facts suggest that 5-HT receptors in the central nervous system are involved in LSD-induced hyperthermia in rabbits. Phenoxybenzamine which inhibited the hyperthermic effect of epinephrine also showed tendency to attenuate the effect of LSD (Table II). According to Elder *et al.* (20) the i.v. injection of phenoxybenzamine attenuated the LSD-induced hyperthermia. However, it is uncertain that adrenergic

receptors are involved in LSD-induced hyperthermia, because α-methyl-p-tyrosine did not attenuate the effect of LSD (13).

Contrary to rabbits, hyperthermic activities of LSD derivatives in rats were not parallel to 5-HT-like activities of these compounds. Therefore, the involvement of 5-HT receptors in LSD-induced hyperthermia is doubtful in rats.

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