J. Pharm. Pharmac., 1975, **27**, 18–22 *Received July* 15, 1975

Some pharmacological actions of 2,5-dimethoxy-4-ethylamphetamine (DOET) in rats and mice

JEN-TZAW HUANG* AND BENG T. HO

Texas Research Institute of Mental Sciences, Houston, Texas 77025 and The University of Texas at Houston, Houston, Texas 77025

DOET, like DOM, exhibited pressor action in rats. This increase of blood pressure was blocked by pretreatment with cinanserin. DOET at high doses decreased the spontaneous locomotor activity of mice at the first hour but increased the activity at the second hour; a low dose was less effective. DOET also increased the rectal temperature of rats and this hyperthermic action was suppressed by pretreating the animals with cinanserin or methysergide. These actions of DOET were compared with those of DOM.

2,5-Dimethoxy-4-methylamphetamine (DOM, STP) has been reported as a strong hallucinogen being 100 times more potent than mescaline (Snyder, Faillace & Hollister, 1967). Substitution of an ethyl group for the methyl group of DOM results in 2,4-dimethoxy-4-ethylamphetamine (DOET) of greater subjective effect such as euphoria and enhanced self-awareness (Snyder, Richelson & others, 1970). We have reported several pharmacological actions of DOM and concluded that DOM differs from amphetamine in every aspect in which its action is likely to be mediated through serotonergic mechanisms (Huang & Ho, 1972, 1973). In this report we present the results of studies on the blood pressure, spontaneous motor activity and body temperature of animals receiving DOET and make comparison with the effects produced by DOM.

MATERIALS AND METHODS

Animals

Male Sprague-Dawley rats (300 to 380 g) were used for blood pressure and body temperature studies. Male Yale Swiss mice (25 to 28 g) were used for the study of spontaneous locomotor activity.

Drugs

DOET was synthesized in our laboratory. Methysergide maleate was supplied to us by Sandoz Pharmaceuticals, Hanover, New Jersey, U.S.A., and phentolamine hydrochloride by Ciba Pharmaceutical Co., Summit, New Jersey, U.S.A. Cinanserin hydrochloride, reserpine and pentobarbitone sodium were purchased from commercial sources.

Blood pressure study

Rats were anaesthetized by intraperitoneal injection of 50 mg kg^{-1} of pentobarbitone sodium. Arterial blood pressure was recorded from a polyethylene cannula placed

*Present address: Department of Pharmacology, University of Minnesota, Minneapolis, Minnesota 55455, U.S.A.

in the left common carotid artery and connected to a pressure transducer (Linear-Core Model P-100) and physiograph (Type DNP-4A), Narco Instrument Co., Houston, Texas, U.S.A.). Injection of DOET in saline was made through the polyethylene cannula in the right external jugular vein. The pithed rats were prepared using the method of Gillespie & Muir (1967). The details of the procedure have been reported previously (Huang & Ho, 1973).

Spontaneous locomotor activity

Mice in groups of two were placed in circular 6-beam photocell activity cages (Woodward Research Co., Hernden, Virginia, U.S.A.). An automatic printout device recorded the accumulative count every 15 min. Control and drug groups were studies simultaneously in two separate cages. Drugs dissolved in saline were injected intraperitoneally into animals with a volume of 0·1 ml per 10 g of body weight. The locomotor activity was measured right after giving DOET and saline.

Body temperature

A Yellow-Spring telethermometer (Model 47) was used to record the rectal temperature of rats. A probe was inserted into the rectum 30 to 60 min before the zero time rectal temperature was taken. DOET was then injected intraperitoneally and the change of rectal temperature with respect to the zero time temperature (Δt) was recorded every 15 min for 150 min. Cinanserin, methysergide and phentolamine were administered intraperitoneally to three other groups of rats 30 min before 1 mg kg^{-1} of DOET.

RESULTS

Table 1 shows that DOET like its homologue DOM exerts a pressor action in rats. This pressor action of DOET was not attenuated by pretreatment with reserpine or phentolamine, and was not diminished when the central nervous system of animals was destroyed by pithing, but was blocked by cinanserin.

At 25 mg kg^{-1}, DOET decreased the spontaneous locomotor activity of mice to less than 30% of the control at 30 and 60 min, but increased the spontaneous loco-

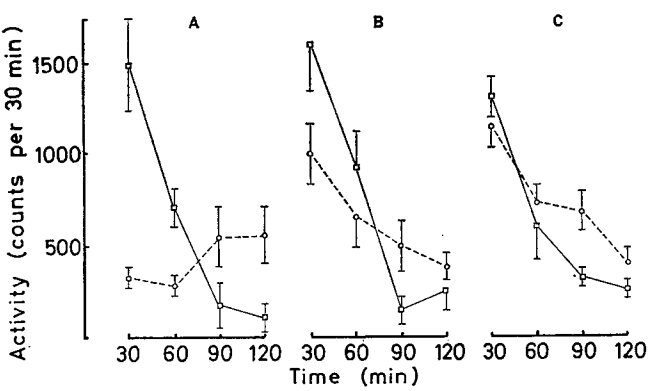

FIG. 1. Effects on the spontaneous locomotor activity of mice by various i.p. doses of DOET. A, 25 mg kg^{-1}; B, 5 mg kg^{-1}; C, 1 mg kg^{-1}. (□——□), saline control group; (○- - - -○), DOET group. Each value represents the mean counts (± s.e.) per 30 min obtained from either 6 (A and C) or 4 (B) groups of two mice.

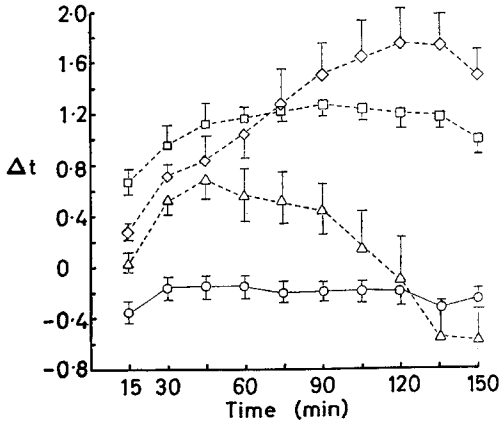

FIG. 2. Effects of various i.p. doses of DOET on the rectal temperatures of rats. (○———○), saline control; (△- - - -△), 0·25 mg kg^{-1}; (□- - - -□), 1 mg kg^{-1}; (◇- - - -◇), 2 mg kg^{-1} DOET. Each value represents the mean (± s.e.) of changes in temperature (Δt) obtained from 6 rats.

motor activity up to 500% at 90 and 120 min (Fig. 1A). Similar but weaker responses were observed with a dose of 5 mg kg^{-1} of DOET (Fig. 1B). DOET at 1 mg kg^{-1} did not affect motor activity at the first hour but caused a slight but significant increase ($P < 0{\cdot}05$) at the second hour (Fig. 1C).

The hyperthermic effect of DOET is shown in Fig. 2. The peak of action appeared at a later time as the dose of DOET increased. After injection of 0·25 mg kg^{-1} of DOET to rats, the maximum increase of temperature was reached in about 45 min, while the peak temperature was at 120 min when 2 mg kg^{-1} of DOET was administered. This hyperthermia, as illustrated in Fig. 3 by 1 mg kg^{-1} of DOET, was suppressed in animals treated 30 min previously with either the 5-HT antagonist, cinanserin (Fig. 3A) or methysergide (Fig. 3B). Phentolamine also blocked the hyperthermic effect of DOET (Fig. 3C).

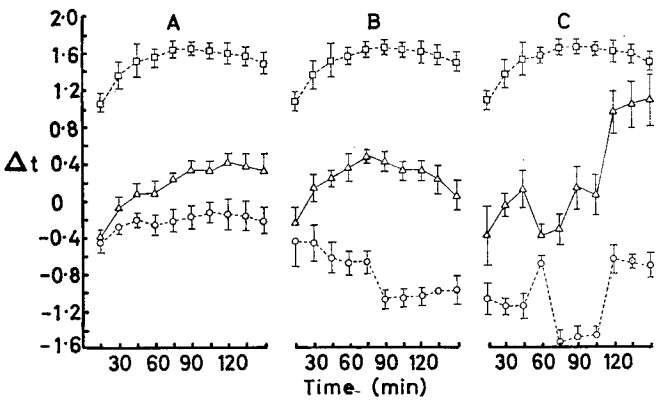

FIG. 3. Effects on DOET-induced hyperthermia in rats by cinanserin (A), methysergide (B), and phentolamine (C). (○- - - -○), the drug (cinanserin, 10 mg kg^{-1}; methysergide, 5 mg kg^{-1}; or phentolamine, 10 mg kg^{-1}) injected i.p. 30 min before measurement of temperature; (△———△), the drug injected 30 min before DOET (1 mg kg^{-1}, i.p.); (□- - - -□), DOET (1 mg kg^{-1}, i.p.). Vertical bars indicate s.e. from six animals. All the points on the drug-DOET curve are significantly different ($P < 0{\cdot}01$) from those on DOET control of the same time interval.

Table 1. *Effects of various treatments on DOET pressor action.*

DOET (μg kg^{-1})	Nontreated	Pithed	Increase in blood pressure (mm Hg) Reserpine* 5 mg kg^{-1}	Phentolamine† 10 mg kg^{-1}	Cinanserin† 2 mg kg^{-1}	Cinanserin† 10 mg kg^{-1}
10	21·6 ± 5·7 (4)	35·6 ± 2·3 (3)	25·6 ± 2·9 (3)	22·7 ± 2·6 (3)	2·0 ± 1·4 (4)	1·5 ± 1·0 (4)
50	41·5 ± 2·7 (4)	50·0 ± 5·8 (3)	51·0 ± 7·0 (3)	33·5 ± 2·8 (3)	11·5 ± 3·3 (4)	3·0 ± 1·9 (4)

Each value represents the mean ± s.e. The numbers of animals are given in parentheses.
*Administered 6 h before DOET.
†Administered 15 min before DOET.

DISCUSSION

The present study indicated that DOET increased the blood pressure in rats; the pressor action of DOET is slightly more potent than DOM (Huang & Ho, 1972). Because of the failure of reserpine or phentolamine to attenuate the pressor action of DOET and the blockage of this pressor action by cinanserin, the mechanism of increase in blood pressure by DOET, like that of DOM, seems to be due to the direct stimulation of the 5-HT receptors in cardiovascular tissue. Moreover, there was no decrease in blood pressure after pithing, indicating that the pressor action of DOET was not mediated through the cns. In another experiment, DOET was shown to produce effects similar to those of DOM on the contraction of rabbit aorta strip and this contraction was blocked by cinanserin (Huang & Ho, 1974).

DOET exerted an effect on the spontaneous locomotor activity of mice similar to that of DOM (Huang & Ho, 1973). Initially, there was an attempt to correlate this action with 5-HT, because the intraperitoneal injection of 5-HT into mice also produced a decreased spontaneous locomotor activity (Brown, 1957; Kobinger, 1958). However, it was later found that pretreatment with either cinanserin or *p*-chlorophenylalanine did not affect the spontaneous locomotor activity of mice injected with DOM; on the other hand, this decreased spontaneous locomotor activity was blocked by pretreatment with (+)-amphetamine (Huang & Ho, 1973). Thus, substances other than 5-HT are possibly involved in the effects of DOM and DOET on the spontaneous locomotor activity.

The results obtained from the study of 5-HT effect on body temperature are inconsistent. Feldberg & Lotti (1967) reported that 5-HT produced hypothermia in rats, whereas according to Sheard & Aghajanian (1968) the amine produced hyperthermia. The present study showed that DOET produced hyperthermia at all doses. This hyperthermic effect can be suppressed by pretreatment of the animals with cinanserin and methysergide, suggesting that the effect of DOET on body temperature of rats is mediated through a 5-HT mechanism. Although the α-adrenoceptor blocking drug phentolamine also blocked the hyperthermic effect of DOET, a high dose of phentolamine has been reported to block 5-HT receptors (Meier, Tripod & Wirz, 1957). In view of all the above findings, it seems that DOET could stimulate 5-HT receptors as has been suggested for the action of DOM by Andén, Corrodi & others (1974). Similar results were obtained on the effect of cinanserin on the hyperthermic action of DOM in rats (Ho, unpublished data).

Studies on the metabolism of DOET and DOM in rats showed the levels of DOET in

blood and brain were higher than those of DOM at the same time intervals (Ho, Estevez and Tansey, to be published). In addition, the half-life in rat blood was longer for DOET than for DOM. This may explain the results of the present study that DOET is more potent than its homologue DOM in the three pharmacological activities. Kulkarni (1973) also reported that DOET seems more potent than DOM in the mice scratching response.

Acknowledgements

The authors wish to thank Ms. Connie Fowler and Ms. Mary McKenna for their technical assistance in the temperature studies. A generous gift of methysergide from Sandoz Pharmaceuticals, Hanover, New Jersey, U.S.A., and phentolamine from Ciba Pharmaceutical Company, Summit, New Jersey, U.S.A., are gratefully acknowledged.

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