Int. J. Neuropharmacol., 1967, 6, 423–429 Pergamon Press. Printed in Gt. Britain.

HYPERTHERMIC EFFECTS OF SOME TRYPTAMINE DERIVATIVES IN RELATION TO THEIR BEHAVIOURAL ACTIVITY

R. W. BRIMBLECOMBE
Ministry of Defence, Chemical Defence Experimental Establishment, Porton Down, Salisbury, Wiltshire, England

(*Accepted* 24 *May* 1967)

Summary—The effects of thirty-six tryptamine derivatives upon the rectal temperature of rabbits and the open-field behaviour of rats are described.

Nine compounds were without effect in either test, a further five evoked behavioural changes in the open-field test but were without effect on rectal temperature. Three of these were, however, too toxic to rabbits to be tested completely. The remaining twenty-two compounds produced significant effects in both test situations and a statistically significant correlation existed between the respective potencies of the compounds in evoking the two effects.

It is suggested that these tryptamines act on the same receptors in the central nervous system as LSD-25 and that the behavioural changes in the open-field test and the hyperthermia are both part of the resulting syndrome.

INTRODUCTION

THERE have been many reports of elevated body temperatures (which for the purposes of this paper will be referred to as hyperthermia) following small doses of lysergic acid diethylamide (LSD-25), particularly in rabbits. HORITA and DILLE (1955) reported that 0·5 μg/kg LSD-25 given by various routes to this species evoked a significant rise in rectal temperature, an effect which appeared to be central in origin. ROTHLIN *et al.* (1956) postulated that the hyperthermia was part of a centrally-induced general excitation of the sympathetic nervous system with the increased excitatory state of the sympathetic centres being a possible major factor in the production of the psychic effects of LSD-25. Direct evidence for the central origin of the effect was produced by NEUHOLD *et al.* (1957) who showed that in decorticated rabbits LSD-25 still had a hyperthermic effect but the effect was almost, or completely, absent after removal of the cerebrum and midbrain, or after decerebration. It was concluded that the probable site of action was the diencephalon.

Studies into the mode of action of LSD-25 in producing this hyperthermia suggest that central nervous system excitation of the type produced by 5-hydroxytryptamine (5-HT) is responsible for the effect. For example HORITA and GOGERTY (1958) showed that the responses to high brain levels of 5-HT were very similar to that of LSD-25 and ELDER and SHELLENBERGER (1962) also produced evidence to suggest that LSD-25 and 5-HT acted at the same, or similar, sites to produce hyperthermia.

HOFMANN (1960) in a review of some chemical and biological aspects of the psychotomimetic substances was able to demonstrate, among a series of lysergic acid derivatives, a reasonable parallelism between the "excitatory syndrome" as evidenced by the hyperthermic effects in rabbits and the psychic effects of the drugs in man. BRIMBLECOMBE *et al.*

(1964) reported that certain tryptamine derivatives were effective in producing hyperthermia in rabbits and, although no exact correlation between this effect and psychic activity in man was possible because of lack of human data, all the compounds known to show activity in man also produced hyperthermia in rabbits.

In the present paper the hyperthermic activity of a larger series of tryptamine derivatives is reported and an attempt is made to correlate this effect with the behaviour-affecting activity of the compounds.

METHODS

(a) *Rabbits*

The rectal temperature measurements were made with copper–constantin thermocouples on male rabbits of the Porton closed colony strain. They were held in restrainers of the type described by PEARCE (1957). The thermocouples were inserted about 4 cm and recording was continuous for 4 hr. Reference thermocouples were insulated and placed in two groups in glass tubes containing liquid paraffin. The glass tubes were immersed in a water bath maintained at 36°C and room temperature was kept as constant as possible at 20°C.

A Honeywell Brown 12-channel recorder was used. This printed out the reading from each channel in turn. The arrangement was such that readings from individual animals or the mean readings from any chosen group of animals could be obtained.

Before injection of the compounds the rabbits were placed in their restrainers and left until their temperatures were steady. This usually took about 1 hr and then injections were made into the marginal vein of the ear. The usual volume of the injection was 1 ml/kg and the solvent used was 0·9% saline at 36°C. Three groups of four rabbits each were used, two groups were given drugs and the third group received a placebo injection of the solvent only. Injections were always made as near as possible to 11·00 hours.

The initial dose of each compound was usually 5 mg/kg. If this had no effect on rectal temperature a subsequent dose of 15·8 mg/kg was used. When 5 mg/kg produced an effect lower doses were given (with a logarithmic ratio between doses of 0·5) until a level was reached at which there was no effect on temperatures.

(b) *Rats*

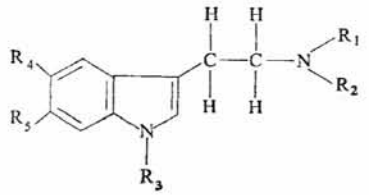
Behavioural effects of the compounds were studied in Hall's open-field test (HALL, 1934). This is a situation where a novel environment is used to evoke a stereotyped pattern of behaviour in rats. Details of the test as used here have been given by BRIMBLECOMBE (1963).

The drugs were administered by subcutaneous injection to groups of eight 190–210 g male albino Wistar rats. The animals were tested in the open-field either 1½ or 3 hr later. A control group was injected with saline alone. For each group the mean number of times rearing, preening and defaecating, the mean number of faecal boluses passed and the mean number of squares traversed were recorded. Possible significant differences between control and treated groups were calculated using Student's *t* test. Decreasing doses were used until an approximate minimal effective dose was reached, this being the lowest dose where any aspect of behaviour was changed significantly.

(c) *Drugs*

The drugs used in these studies are listed in Table 1 which also shows the solvent used in the animal tests. Doses are given in terms of the salt. With the exception of 5-hydroxy-

TABLE 1. TRYPTAMINE DERIVATIVES USED

General formula 

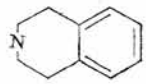
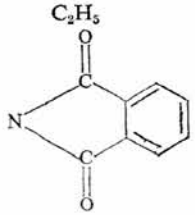
Compound number	R_1	R_2	R_3	R_4	R_5
1	H	CH_3	H	H	H
2	CH_3	CH_3	H	H	H
3	H	C_2H_5	H	H	H
4	C_2H_5	C_2H_5	H	H	H
5	H	nC_3H_7	H	H	H
6	nC_3H_7	nC_3H_7	H	H	H
7	H	iC_3H_7	H	H	H
8	iC_3H_7	iC_3H_7	H	H	H
9	H	nC_4H_9	H	H	H
10	nC_4H_9	nC_4H_9	H	H	H
11	H	iC_4H_9	H	H	H
12	iC_4H_9	iC_4H_9	H	H	H
13	H	sC_4H_9	H	H	H
14	H	CH_2Ph	H	H	H
15	CH_2Ph	CH_2Ph	H	H	H
16	H	$CH_2Ph(pCl)$	H	H	H
17	H	$CH_2Ph(pOCH_3)$	H	H	H
18	H	CH_2CH_2Ph	H	H	H
19	H	$CH(CH_3)Ph$	H	H	H
20			H	H	H
21	CH_2Ph	$COCH_3$	H	H	H
22	CH_2Ph	C_2H_5	H	H	H
23	+ $N(CH_3)_3$		H	H	H
24	+ $N(C_2H_5)_3$		H	H	H
25	CH_3	CH_3	H	OH	H
26	C_2H_5	C_2H_5	H	OH	H
27	C_2H_5	C_2H_5	H	OCH_2Ph	H
28		H	H	H	H
29	H	H	H	OH	H
30	H	H	CH_2Ph	H	H
31	H	H	$CH_2CH_2N(C_3H_7)_2$	H	H

TABLE 1—*Continued*

Compound number	R_1	R_2	R_3	R_4	R_5
32			H	H	OCH_3
33			H	OH	H
34			H	OCH_2Ph	H
35			H	H	H
36			H	OCH_3	H

tryptamine and bufotenine (purchased from Light and Co. Ltd.) all compounds were synthesised by Dr. D. F. Downing and Dr. R. R. Hunt (BRIMBLECOMBE *et al.*, 1964; HUNT and BRIMBLECOMBE, 1967).

RESULTS

Preliminary studies with groups of control or placebo-injected rabbits showed that, after the period of settling down, there were very rarely fluctuations of more than $\pm$ 0·5°C from the mean level of rectal temperature. Therefore, in the drug studies, changes of more than 0·5°C were regarded as being significant.

Table 2 shows the minimal dose of each drug which produced a mean rise in rectal temperature of more than 0·5°C. The minimal dose required to produce a significant change in the open-field behaviour of rats is also given.

Of the thirty-six compounds examined, nine (Numbers 1, 11, 13, 20, 21, 23, 24, 30, 31) had no effect in the open-field test at the maximum dose level used (50 mg/kg). None of these compounds had any effect on rabbit rectal temperature at the maximum dose level of 15·8 mg/kg. An additional five compounds were also without effect on rectal temperature although they showed activity in the open-field test. Three of these (Compounds 9, 28 and 35) were toxic to rabbits so that it was not possible to carry out the full procedure of testing in the species. The two remaining compounds (Numbers 15 and 29) were inactive at 15·8 mg/kg in the rectal temperature test but active at 15 and 4 mg/kg respectively in the open-field test.

The remaining twenty-two compounds were active in both tests and a coefficient of correlation was calculated between minimal effective doses in each situation. This was + 0·48, indicating a positive correlation between the activity of the compounds in the two tests significant at the 95% level of probability.

TABLE 2. SUMMARY OF PHARMACOLOGICAL RESULTS

Compound number	Rabbit rectal temperature experiments					Minimal effective dose, Hall's open-field (mg/kg)
	Minimal effective dose (mg/kg)	Mean time to onset of effect (min)	Mean time to peak effect (min)	Mean duration of effect (min)	Mean maximum rise in temp (°C)	
1	15·8*	—	—	—	—	>50
2	1·58	18	60	112	0·8	2
3	1·58	14	32	165	0·8	5
4	1·58	30	80	240	0·8	2
5	15·8	18	80	240	2·3	10
6	1·58	74	121	180	0·6	5
7	5·0	16	67	240	0·7	30
8	1·58	16	145	240	1·7	5
9	15·8†	—	—	—	—	2
10	5	20	49	240	0·7	5
11	15·8*	—	—	—	—	>50
12	15·8	12	55	240	1·2	50
13	15·8*	—	—	—	—	>50
14	5	24	30	240	0·6	0·5
15	15·8*	—	—	—	—	15
16	15·8	18	30	189	0·8	20
17	15·8	20	23	210	0·7	5
18	15·8	28	58	160	0·9	10
19	5	16	52	240	0·9	15
20	15·8*	—	—	—	—	>50
21	15·8*	—	—	—	—	>50
22	5	6	36	240	1·0	50
23	15·8†	—	—	—	—	>50
24	15·8*	—	—	—	—	>50
25	5	10	132	240	3·5	15
26	5	45	134	240	1·9	5
27	5	26	240	240	1·7	5
28	15·8†	—	—	—	—	20
29	15·8*	—	—	—	—	4
30	15·8*	—	—	—	—	>50
31	15·8*	—	—	—	—	>50
32	15·8	12	32	150	1·3	50
33	1·58	10	110	240	2·8	0·25
34	5	16	104	160	0·7	10
35	0·5†	—	—	—	—	5
36	0·158	2	82	225	3·3	0·1

*Inactive at this and all lower doses.
†Inactive at lower doses but toxic at this dose.

To indicate the pattern of the temperature rise following each compound Table 2 also shows the time to onset of the effect, the time to peak, the duration and the extent of the rise in temperature. It was not considered profitable to attempt to calculate any correlations based on these values since some adjustment would have to have been made to allow for the different effective dose levels and until there is a clearer understanding of the relationship between dose and response any such adjustment would have been purely arbitrary.

It is, however, perhaps worth noting that following injection of the most active compound (Number 36) the time taken to reach a significant elevation in temperature was only 2 min, the shortest time for any compound.

DISCUSSION

These studies show that, in the series of tryptamine derivatives used, there was a reasonably good parallelism between ability to affect the behaviour of rats in the open-field situation and to produce an increase in the rectal temperature of rabbits. Where effects occurred in both species there was a statistically significant correlation between the respective potencies of the various compounds in producing the two effects. Potency in this context means reciprocal of the minimal effective dose. Of the remaining compounds nine were inactive in both tests but five were active in the open-field test while having no effect on rabbit rectal temperature at the doses tested. Three of these five were relatively toxic to rabbits and because they could not be fully tested it is not possible to say whether in fact a discrepancy existed. The remaining two compounds, however, do not appear to conform to the general pattern. These compounds are N,N-dibenzyl tryptamine and 5-hydroxytryptamine or serotonin. It is known that 5-hydroxytryptamine does not pass the blood–brain barrier (UDENFRIEND *et al.*, 1957) and so the effects of this drug in the open-field situation are presumably due to peripheral actions. Whether the same explanation applies to N,N-dibenzyl tryptamine is not known. Indeed there is no direct evidence from these studies to indicate the origin of the effects of any of the drugs but indirect evidence which suggests a central origin is provided by the fact that compounds 2 and 4, which were active both behaviourally and in causing a rise in body temperature, lost both activities when quaternised (cf. compounds 23 and 24), and so became incapable of passing the blood–brain barrier.

No other clear-cut relationship between chemical structure and pharmacological activity emerged, although a few trends were apparent. Thus, among compounds with lower alkyl substituents on the terminal N atom, the dialkyl compounds tended to be more active than the corresponding monosubstituted compounds. Compounds with substituents in the benzene ring or on the indole N atom were less active than those with no substituents.

The results presented in this paper, while not conclusive, lend weight to the argument that the hyperthermic effects of these tryptamine derivatives, as well as of LSD-25, form part of a syndrome which includes behavioural effects. Whether this syndrome is specific to the tryptamines or might be produced by other drugs like amphetamine which might also affect the hypothalmus is not, at this stage, clear. Although two compounds at least produced changes in open-field behaviour without affecting rectal temperature it would seem that the rabbit rectal temperature test constitutes a simple and reasonable satisfactory screening procedure for evaluating the psychotropic activity of these drugs, particularly since a correlation exists between potency in elevating rectal temperature and in affecting behaviour.

VANE *et al.* in 1961 suggested that tryptamine receptors are widely scattered throughout the central nervous system. TEDESCHI *et al.* (1959) had proposed earlier that tryptamine and 5-HT shared common pharmacological receptors in the central nervous system. If such receptors exist then it is presumably with these that the tryptamine derivatives interact to produce the effects on behaviour and on body temperature and it seems likely that LSD-25 also interacts with the same receptors. It should be mentioned, however, that other workers (BRADLEY and MARLEY, 1965) have shown certain differences between certain actions of LSD-25 and the tryptamines. In particular it appears that for arousal to occur with LSD-25 sensory input is essential whereas this is not the case with the tryptamines.

Not all the compounds examined here have been tested in man but there are reports in the literature of psychotomimetic actions of N,N-dimethyltryptamine, compound 2 (ROSENBERG *et al.*, 1964; and SAI-HALASZ, 1962), N,N-diethyltryptamine, compound 4 (SZARA, 1961; and BOSZORMENYI *et al.*, 1959), N,N-dipropyltryptamine, compound 6 (SZARA, 1961) and 5-hydroxy-N,N-dimethyltryptamine compound, 25 (FABING and HAWKINS, 1956). In the present studies all these compounds affected both rectal temperature and open-field behaviour.

Acknowledgement—Valuable assistance in these experiments was given by Mr. J. W. BLACKBURN and Mr. D. C. PARKES.

REFERENCES

BOSZORMENYI, Z., DER, P. and NAGY, T. (1959). Observations on the psychotogenic effect of N,N-diethyltryptamine, a new tryptamine derivative. *J. ment. Sci.* **105:** 171–181.

BRADLEY, P. B. and MARLEY, E. (1965). Effect of tryptamine and tryptamine homologues on cerebral electrical activity and behaviour in the cat. *Br. J. Pharmac.* **24:** 659–674.

BRIMBLECOMBE, R. W. (1963). Effects of psychotropic drugs on open-field behaviour in rats. *Psychopharmacologia* **4:** 139–147.

BRIMBLECOMBE, R. W., DOWNING, D. F., GREEN, D. M. and HUNT, R. R. (1964). Some pharmacological effects of a series of tryptamine derivatives. *Br. J. Pharmac.* **23:** 43–54.

ELDER, J. T. and SHELLEHBERGER, M. K. (1962). Antagonism of lysergic acid diethylamide (LSD)-induced hyperthermia. *J. Pharmac. exp. Ther.* **136:** 293–297.

FABING, H. D. and HAWKINS, J. R. (1956). Intravenous bufotenine injection in the human being. *Science* **123:** 886–887.

HALL, C. S. (1934). Emotional behaviour in the rat: I. Defecation and urination as measures of individual differences in emotionality. *J. comp. Psychol.* **18:** 385–403.

HOFMANN, A. (1960). Psychotomimetics: chemical, pharmacological and medical aspects. *Svensk. kem. Tidskr.* **72:** 723–747.

HORITA, A. and DILLE, J. M. (1955). The pyretogenic effect of lysergic acid diethylamide. *J. Pharmac. exp. Ther.* **113:** 29.

HORITA, A. and GOGERTY, J. H. (1958). The pyretogenic effect of 5-hydroxytryptophan and its comparison with that of LSD. *J. Pharmac. exp. Ther.* **122:** 195–200.

HUNT, R. R. and BRIMBLECOMBE, R. W. (1967). Synthesis and biological activity of some ring-substituted tryptamines. *J. med. Chem.* (in the press).

NEUHOLD, K., TAESCHLER, M. and CERLETTI, A. (1957). Beitrag sur zentralen Wirkung von LSD: Versuche über die Lokalisation von LSD-Effekten. *Helv. physiol. pharmac. Acta* **15:** 1–7.

PEARCE, K. A. (1957). Simple devices for the restraint of rabbits, rats, mice and guinea pigs. *J. Physiol., Lond.* **135:** 39P.

ROSENBERG, D. E., ISBELL, H., MINER, E. J. and LOGAN, C. R. (1964). The effect of N,N-dimethyltryptamine in human subjects tolerant to lysergic acid diethylamide. *Psychopharmacologia.* **5:** 217–227.

ROTHLIN, E., CELETTI, A., KONZETT, H., SCHALCH, W. R. and TAESCHLER, N. (1956). Central vegetative effects of lysergic acid diethylamide. *Experientia* **12:** 154–155.

SAI-HALASZ, A. (1962). The effect of antiserotonin on the experimental psychosis induced by dimethyltryptamine. *Experientia* **63:** 137–138.

SZARA, S. (1961). Correlation between metabolism and behavioural action of psychotropic tryptamine derivatives. *Biochem. Pharmac.* **8:** 32.

TEDESCHI, D. H., TEDESCHI, R. E. and FELLOWS, E. J. (1959). The effects of tryptamine on the central nervous system, including a pharmacological procedure for the evaluation of iproniazid-like drugs. *J. Pharmac. exp. Ther.* **126:** 223–232.

UNDENFRIEND, S., WEISSBACH, H. and BOGDANSKI, D. F. (1957). Increase in tissue serotonin following administration of its precursor 5-hydroxytryptophan. *J. biol. Chem.* **224:** 803–810.

VANE, J. R., COLLIER, H. O. J., CORNE, S. J., MARLEY, E. and BRADLEY, P. B. (1961). Tryptamine receptors in the central nervous system. *Nature, Lond.* **191:** 1068–1069.