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Comparative Study of 1-Cyclohexyl-4-(1,2-Diphenylethyl)-Piperazine and Its Enantiomorphs on Analgesic and other Pharmacological Activities in Experimental Animals

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Abstract—The analgesic activity of (±)-1-cyclohexyl-4-(1,2-diphenylethyl)-piperazine (MT-45) was comparable to that of morphine. The activity of the S(+)-isomer was 1.14 to 1.97 times in mice and 1.00 to 1.23 times in rats as potent as MT-45, and 18.3 to 61.6 times as potent as the R(−)-isomer, which was approximately comparable to that of Spa. The hyperglycemic and miotic activities of MT-45 and its S(+)-isomer in rabbits were negligible or very low, though they showed potent morphine-like activities. On the other hand, the R(−)-isomer showed no or very weak effects on those, while Spa showed definite effects. These results suggest that the modes of action of MT-45 and its enantiomorphs are partly different from those of morphine and Spa, and it may be concluded that MT-45 belongs to a new series of compounds having a potent analgesic activity.

Introduction

A number of morphine derivatives and many compounds with a partial chemical structure of the morphine molecule have been synthesized for developing potent analgesics. When the narcotic analgesics which contain an asymmetric carbon atom are resolved, one enantiomer usually retains most of the analgesic activity, *i.e.* morphine-like analgesics possess highly stereoselectivity in the interaction with analgesic-receptors (1–3).

During the investigation of diphenylethylpiperazine derivatives in our laboratory, it was found that 1-cyclohexyl-4-(1,2-diphenylethyl)-piperazine, MT-45 (Fig. 1), possessed a morphine-like analgesic action (4). MT-45, bearing a common N-substituted 1,2-diphenylethylamine moiety to (*l*)-1,2-diphenyl-1-dimethylaminoethane(Spa), has an asymmetric carbon atom at the β-position related to that of Spa. Fujimura *et al.* (5, 6) have reported that Spa, the R(−)-

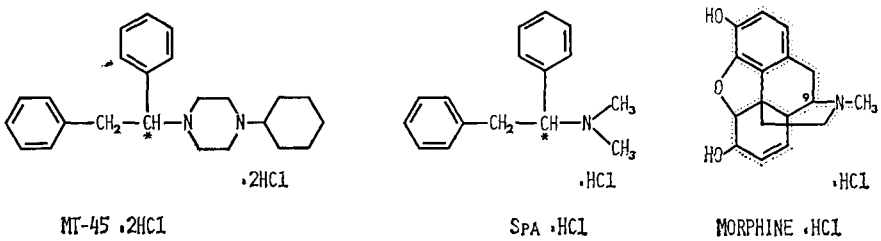

FIG. 1

Chemical structures of 1-cyclohexyl-4-(1,2-diphenylethyl)-piperazine (MT-45), 1,2-diphenyl-1-dimethylaminoethane (Spa) and morphine.
*: asymmetrical carbon.

enantiomer, is approximately one-tenth as active as morphine, while the S(+)-enantiomer of Spa is virtually inactive, and Nakazaki *et al.* (7) have described a stereochemical resemblance of Spa to morphine. However, the authors found the S(+)-enantiomer of MT-45 to have more potent analgesic activity than its R(−)-enantiomer, and the R(−)-enantiomer to be approximately as active as Spa.

The purpose of the present study is to determine and compare the analgesic and morphine-like activities of MT-45 and its enantiomorphs in laboratory animals.

Methods

Analgesic Assay.

Thermal pain was induced by radiating heat light on the tail blacked with a black ink of male mice (9–12 g) of ddN strain or male rats (90–110 g) of Wistar strain using the modified apparatus of D'Amour-Smith (8) according to the procedure of Nakamura *et al.* (9). The animals showing a tail-flick response time of 4–6 sec were selected; the tail-flick response time of the animals was measured 6 times at 30 min intervals after drug treatment with an arbitrary cutoff time of 15 sec. The analgesic ED_{50}-value was calculated from the number of positive animals showing the response time prolonged more than 50 % in rats and 100 % in mice compared with each preceding value.

Mechanical pain was induced by pressing the tail of male mice (24–28 g) of STDddY strain or male rats (90–110 g) of Wistar strain using an apparatus deviced by us, which consisted of a fixed plate and a movable rod with a sharp tip (1 mm wide and 5 mm long). The pain threshold was measured as mm (1 mm = 12.5 g pressure), and the analgesic ED_{50}-value was calculated from the number of positive animals showing a pain threshold of 40 mm or more (normal value is about 20 mm).

Electrical stimulation was given on the base of the tail of male mice (18–22 g) of ddN strain according to the modified method of Nilsen (10). The analgesic ED_{50}-value was calculated from the number of positive mice showing the response time prolonged more than 50 % compared with the preceding value.

Chemical pain was induced by an i.p. injection of 0.1 ml/10 g body weight of 0.03 % phenylquinone in 5 % aqueous ethanol in female mice (18–22 g) of ddN strain (11). Drugs were given 30 min before challenge of phenylquinone. Six to 12 mice were used for a dose, and statistical analysis was done according to the Litchfield-Wilcoxon method (12).

Gastrointestinal Propulsion.

Inhibition of gastrointestinal propulsion was measured using the technique of the charcoal meal test in male mice (20–22 g) of ddN strain (6). Mice were fasted for 4 hr before the test, and each drug was given s.c. 30 min before the administration of the charcoal meal (charcoal: gum tragacanth: water = 1 : 0.3 : 20). The intestines were cut off from pylorus to anus 30 min after the meal, and the proportion of intestines traversed was measured immediately. Five mice were used for each dose.

Body Temperature.

Male rats (170–250 g) of Wistar strain were maintained in separate cages in an air-conditioned room at 23 ± 1° C for 5 days prior to the experiment. The rectal temperature was measured with a thermometer before and every hr for 5 hr after the s.c. injection of each drug (9, 13). Five rats were used for each dose.

Pupillary Sizes.

The pupil sizes of male mice (17–23 g) of ddN strain were measured with a stereoscopic microscope at a distance of 120 cm from a lamp of 40 w (14). Five mice were used for each dose. The pupil sizes of male rabbits (2.5–4.5 kg) were measured before and 0.5, 1, 2, 3, 4 and 5 hr after the s.c. injection of each drug according to the method of Suda (15). Four rabbits were used for each dose.

Plasma Glucose Levels.

Male rabbits (2.5–4.5 kg) were fasted for 18 hr prior to the experiment. Plasma glucose concentration was determined before and every hr for 5 hr after the s.c. injection of each drug according to the method of Hagedron-Janssen (N-2b of Autoanalyzer methodology). Four rabbits were used for each dose.

Acute Lethal Toxicity.

Acute lethal toxicity was determined by i.v., s.c. and p.o. routes in male mice (18–22 g) of ddN strain and male rats (100–150 g) of Wistar strain. The mortality was observed for 7 days. Five to 10 animals were used for each dose. The LD_{50}-value was calculated according to the Litchfield-Wilcoxon method (12).

Materials.

The following drugs were used: morphine hydrochloride (Dainippon Pharm. Co., Ltd.), (*l*)-1,2-diphenyl-1-dimethylaminoethane (Spa) hydrochloride (Santen Pharm. Co., Ltd.), (±)-1-cyclohexyl-4-(1,2-diphenylethyl)-piperazine (MT-45) dihydrochloride (4), S(+)-1-cyclohexyl-4-(1,2-diphenylethyl)-piperazine(S-isomer) dihydrochloride (4) and R(−)-1-cyclohexyl-4-(1,2-diphenylethyl)-piperazine(R-isomer) dihydrochloride (4). All doses are expressed as the weight of the salt used.

Results

Analgesic Activity.

The analgesic activity of MT-45 in mice and rats was compared with that of morphine and Spa. As shown in Table I, the analgesic ED_{50}-values of MT-45 were 3.09, 2.15, 1.54 and 2.24 mg/kg, s.c., in mice against thermal, mechanical, electrical and chemical pains, respectively, and the activity was almost as potent as that of morphine except against the chemical pain. In rats, analgesic ED_{50}-values of MT-45 were 6.62 and 0.73 mg/kg, s.c., against the thermal and mechanical pains, respectively. MT-45 was more effective than morphine against mechanical pain, but less effective against thermal pain. After oral administration, the analgesic activity of MT-45 was equivalent to or more potent than that of morphine except against electrical and chemical pains in mice. The analgesic activity of Spa was about 1/9 to 1/15 as potent as that of MT-45 against thermal, mechanical and electrical pains in mice and about 1/6 to 1/57 against thermal and mechanical pains in rats after s.c. application. Spa did not show analgesic activity against thermal pain up to toxic doses after oral application in mice and rats, and against mechanical pain in rats.

The analgesic ED_{50}-values of the S-isomer were 1.92, 1.09, 0.91 and 1.97 mg/kg, s.c., in mice against thermal, mechanical, electrical and chemical pains, respectively; the S-isomer was 18.3 to 42.1 times as potent as the R-isomer (Table II). In rats, the analgesic ED_{50}-values of the S-isomer were 0.73 and 5.39 mg/kg, s.c., against mechanical and thermal pains, respectively; the S-isomer was 61.6 and more than 13.9 times as potent as the R-isomer, respectively. After oral application, the analgesic ED_{50}-values of the S-isomer were 20.9, 5.51, 14.8 and 10.6 mg/kg in mice against thermal, mechanical, electrical

TABLE I

Analgesic activity of MT-45, morphine and Spa in mice and rats

Species and Stimulus	Route	Analgesic ED_{50} in mg/kg (95 % confidence limits)					
		MT-45 · 2HCl		Morphine · HCl		Spa · HCl	
		ED_{50}	*n*	ED_{50}	*n*	ED_{50}	*n*
in *Mice*							
Thermal	s.c.	3.09 (2.21–4.95)	77	2.39 (1.78–3.20)	40	46.6 (29.0–66.9)	27
	p.o.	20.9 (16.1–28.1)	54	29.4 (18.9–49.0)	41	240.0 < inactive	
Mechanical	s.c.	2.15 (1.70–2.48)	40	2.41 (1.77–3.29)	45	19.4 (15.5–24.0)	32
	p.o.	11.9 (8.50–17.6)	36	15.4 (8.93–26.5)	30	68.6 (49.9–93.5)	33
Electrical	s.c.	1.54 (1.06–2.07)	24	1.22 (0.67–2.05)	28	17.9 (11.6–28.3)	28
	p.o.	30.8 (21.8–43.4)	24	7.70 (10.1–24.8)	24	100.0 <	
Chemical	s.c.	2.24 (1.90–2.69)	24	0.58 (0.43–0.77)	18	3.86 (2.10–7.06)	18
	p.o.	12.5 (6.29–21.8)	26	4.20 (2.61–6.77)	18	52.3 (33.5–81.5)	24
in *Rats*							
Thermal	s.c.	6.62 (4.12–10.9)	30	3.79 (3.03–4.40)	24	36.9 (30.5–44.6)	25
	p.o.	29.5 (19.8–49.1)	53	41.0 (27.7–55.8)	55	240.0 < inactive	
Mechanical	s.c.	0.73 (0.37–1.17)	30	1.17 (0.65–2.28)	48	42.0 (30.1–56.1)	30
	p.o.	36.4 (27.1–53.0)	35	32.0 (25.2–41.5)	30	240.0 < inactive	

The analgesic effects of MT-45 and both isomers after s.c. application attained the highest peaks within 30 min, followed by significant activities lasting for 60 min or more (Fig. 2).

Gastrointestinal Propulsion.

Subcutaneous administration of 3 and 10 mg/kg of MT-45 significantly ($P < 0.01$) reduced the transit of charcoal; its potency was somewhat weaker than that of morphine, as shown in Fig. 3. The S-isomer showed a somewhat more potent inhibitory effect compared with MT-45. The R-isomer was about 1/10 as active as the S-isomer, and its activity was comparable to that of Spa.

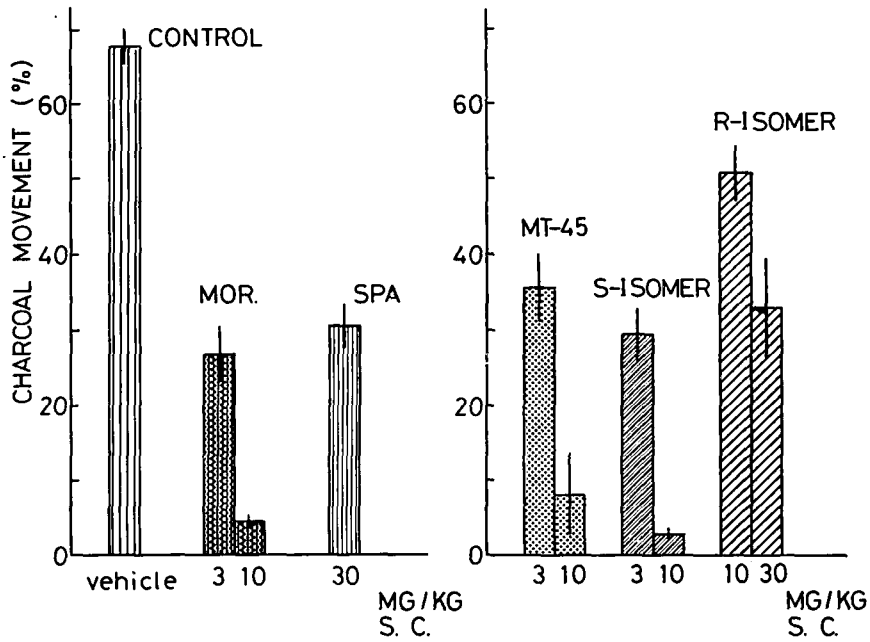

FIG. 3

Effects of MT-45, the S-isomer, the R-isomer, morphine and Spa on the propulsion of charcoal meal in mice.

Each column represents the mean ± S.E. from 5 mice.

The vertical represents the proportion of the intestine traversed by the charcoal in 30 min. All doses are expressed as the weight of the used salt.

Pupillary Size.

The mydriatic activity of MT-45 was superior to that of morphine at 10 mg/kg, s.c., but much less at 3 mg/kg, s.c., in mice (Fig. 4A, 4B). At a dose of 10 mg/kg, s.c., the activity of the S-isomer was comparable to that of MT-45. The mydriatic

activity of the R-isomer was almost negligible at 30 mg/kg, s.c., while 30 mg/kg, s.c., of Spa was approximately comparable to 3 mg/kg, s.c., of morphine.

In rabbits, the s.c. administration of 10 mg/kg of morphine caused a miotic effect ($P < 0.001$), but Spa showed a mydriatic action ($P < 0.001$) at 30 mg/kg, as shown in Fig. 4C. On the contrary, neither MT-45 nor its isomers showed any effect on the pupil sizes of rabbits (Fig. 4D).

Body Temperature.

Subcutaneous administration of 10 mg/kg of MT-45 caused an increase of the rectal temperature by 1.02° C at the peak effective time in rats ($P < 0.05$), as shown in Fig. 5. The hyperthermic activity of MT-45 was much less than that of morphine, and comparable to that of the S-isomer. Thirty mg/kg, s.c., of Spa caused an increase in the rectal temperature by 0.64° C at the peak effective time ($P < 0.05$), but the R-isomer did not cause any change at the same dose of 30 mg/kg.

Plasma Glucose Levels.

As shown in Fig. 6, subcutaneous administration of morphine caused a remarkable rise (135.7 %) in the plasma glucose level at 10 mg/kg ($P < 0.001$), and Spa raised the level by 51.6 % ($0.05 < P < 0.1$) in rabbits at 30 mg/kg. The hyperglycemic activity of MT-45 was comparable to that of the S-isomer and much weaker than that of morphine. The R-isomer (30 mg/kg) did not alter the plasma glucose levels.

Respiration.

The respiratory effect after i.v. administration of MT-45 and both isomers was investigated in anesthetized rabbits (2.5–3.5 kg). MT-45 and the S-isomer caused a respiratory depression by 59 % and 57 % at 1 mg/kg, respectively, but the R-isomer did not cause any respiratory depression even at 5 mg/kg. Morphine caused a respiratory depression by 63 % at 3 mg/kg.

Local Anesthetic Activity.

The local anesthetic activity of MT-45 and both isomers was investigated according to the method of the corneal reflex in guinea-pigs (300–350 g). Mean effective concentrations of MT-45, the S-isomer and the R-isomer were 0.092, 0.160 and 0.03 %, respectively. Those of morphine, Spa and procaine were 2.00, 1.00 and 0.27 %, respectively. Accordingly, the local anesthetic activity of the R-isomer was about 5 to 9 times as potent as that of the S-isomer and procaine, respectively.

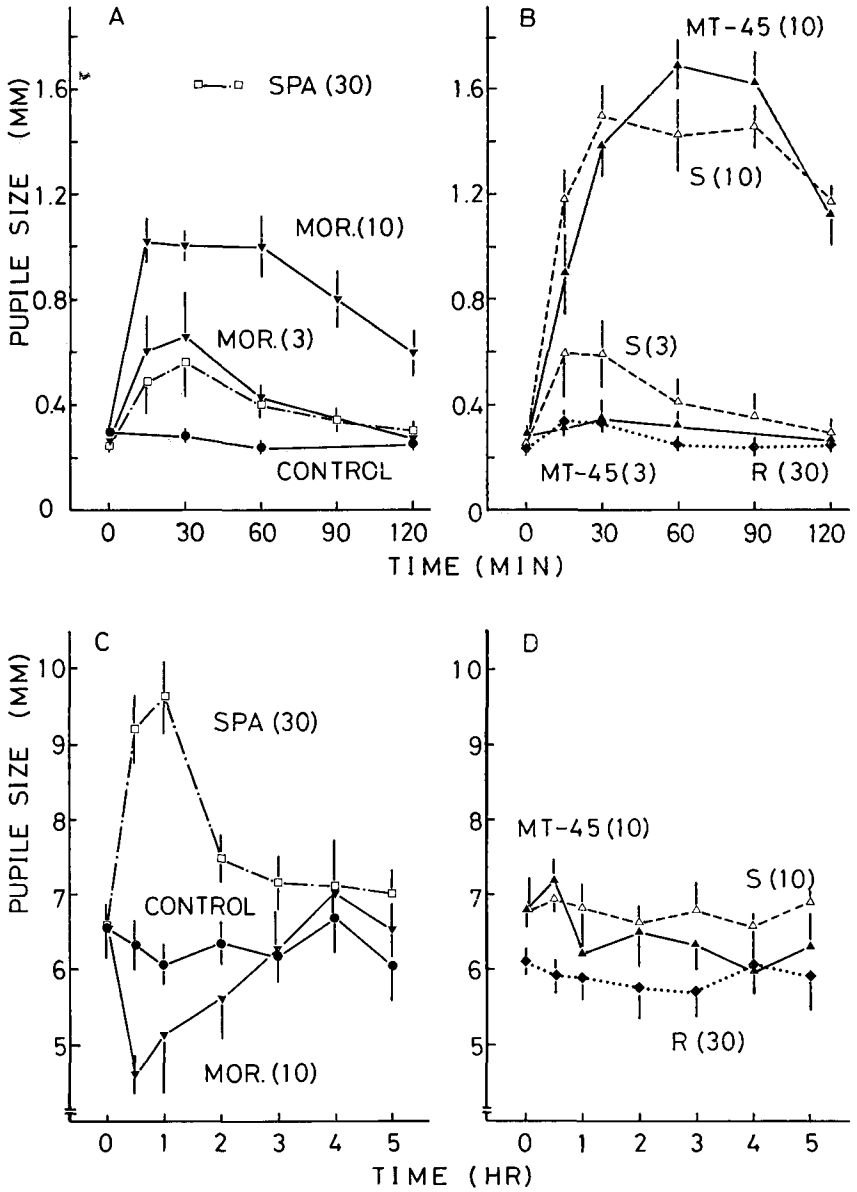

FIG. 4

Effects of MT-45, the S-isomer, the R-isomer, morphine and Spa on the pupillary size in mice and rabbits.

A and B: in *mice*, C and D: in *rabbits*.

( ): mg/kg, s.c. as the weight of the used salt.

R: the R-isomer, S: the S-isomer, MOR.: morphine.

Each points represents the mean ± S.E. from 5 mice or 4 rabbits.

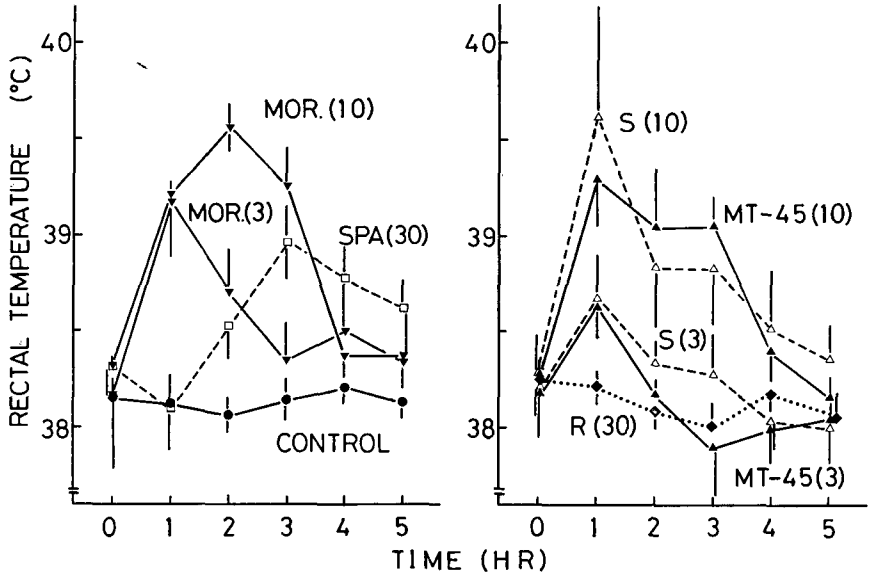

FIG. 5

Effects of MT-45, the S-isomer, the R-isomer, morphine and Spa on the body temperature in rats.

Each points represents the mean ± S.E. from 5 rats.

See Fig. 4 footnotes.

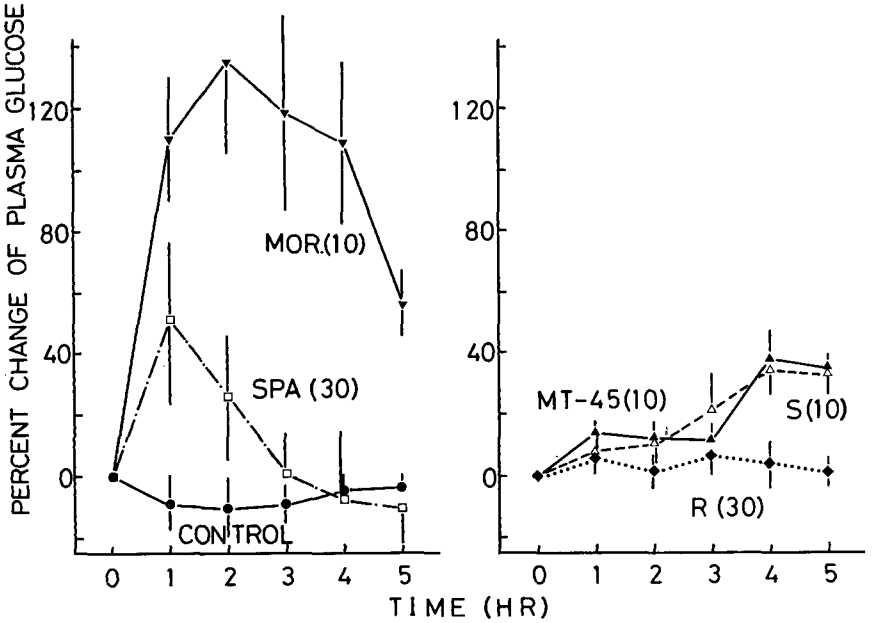

FIG. 6

Effects of MT-45, the S-isomer, the R-isomer, morphine and Spa on plasma glucose levels in rabbits.

Each points represents the mean ± S.E. from 4 rabbits.

See Fig. 4 footnotes.

Toxicity.

LD_{50}-values are shown in Table III and IV. The animals receiving toxic doses of MT-45 or the S-isomer died with symptoms of severe sedation, muscle rigidity and dyspnea. In lower doses, the R-isomer caused sedation, while the S-isomer and MT-45 caused excitation. MT-45 and the S-isomer showed a characteristic tail elevation like morphine and Spa, but the R-isomer did not. The difference in lethal toxicity among enantiomorphs was not observed by the i.v. route. By both s.c. and oral routes, the S-isomer showed higher toxicity than the racemic form, MT-45. However, the R-isomer showed the highest toxicity in relation to its analgesic activity.

Discussion

It is well known that among morphine-like analgesics one enantiomer is usually more active than its mirror image (3). Unnatural (+)-morphine is virtually inactive as an analgesic (16, 17); the absolute configuration of morphine has been determined to be 5R:6S:9R:13S:14R (18, 19). Stereoselectivity on analgesic activity is exhibited by the less complex morphinan analgesics and analgesic antagonists, and benzomorphan analgesics (3). The *levo* enantiomers of these analgesics bear the same absolute configuration as morphine or nalorphine with respect to the C-9 asymmetric centre, and retain most of the analgesic activity (3, 20, 21). Furthermore, a simpler analgesic, Spa, has the same configuration as morphine with respect to the C-9 centre of morphine, and its antipode is almost inactive (7, 22).

On the contrary, the S(+)-isomer of MT-45 showed more potent analgesic and pharmacological activities than those of the R(−)-isomer, having a partial structure of Spa. The analgesic activity of the S-isomer was s.c. 18.3 to 42.1 times and orally 2.8 times as potent as that of the R-isomer in mice (Table II). The more active enantiomer of MT-45 bears the reverse absolute configuration as Spa and as morphine with respect to the C-9 centre of morphine. The following three cases may be assumed: (1) if MT-45 is a pharmacological analogue of Spa and morphine, the 9R-configuration of morphine is not essential to exhibit the analgesic activity; (2) if MT-45 is a pharmacological analogue of morphine, but not of Spa, the conformation of the S-isomer resembles that of morphine, and (3) if MT-45 is not a pharmacological analogue of Spa and morphine, the mode of interaction of the S-isomer with analgesic receptors is different from that of morphine-like analgesics.

If MT-45 is a pharmacological analogue of 1,2-diphenylethylamine and analgesia is brought about by the same mode of interaction of Spa with analgesic receptors, the analgesic activity should be retained with its R-isomer as with Spa. Therefore, MT-45 may not belong to a series of 1, 2-diphenylethylamine, at least, in respect of the mode of interaction with analgesic receptors, *i.e.* the first assumption is denied.

TABLE III

Acute lethal toxicity of MT-45, morphine and Spa in mice and rats

Species	Route	LD_{50} (on 7 days) in mg/kg (95 % confidence limits)					
		MT-45 · 2HCl		Morphine · HCl		Spa · HCl	
		LD_{50}	*n*	LD_{50}	*n*	LD_{50}	*n*
Male mice	p.o.	329 (264–501)	36	1402 (926–2122)	48	176 (139–222)	40
	s.c.	743 (548–762)	51	560 (517–606)	30	104 (88.6–123)	56
	i.p.	58.4 (49.5–72.3)	40				
	i.v.	17.8 (15.1–18.9)	20	204 (132–328)	20	32.6 (18.8–47.5)	20
Male rats	p.o.	150 (105–198)	30	335 (229–490)	52	300 ca.	
	s.c.	136 (99.3–199)	36			148 (120–183)	26
	i.v.	7.8 (5.5–16.4)	24				

TABLE IV

Acute lethal toxicity of two enantiomorphs of MT-45 in mice and rats

Species	Route	LD_{50} (on 7 days) in mg/kg (95 % confidence limits)			
		S(+)-isomer · 2HCl		R(−)-isomer · 2HCl	
		LD_{50}	*n*	LD_{50}	*n*
Male mice	p.o.	274 (180–361)	50		
	s.c.	320 (263–389)	30		
	i.v.	18.5 (16.8–20.3)	30	17.9 (15.4–20.1)	30
Male rats	i.v.	8.0 (6.0–10.2)	20	12.9 (11.9–13.9)	20

Nakazaki (22) has reported the conformational resemblance between Spa and morphine with respect to the A and C-rings of morphine. However, the results with isomorphinan (23) and benzomorphan (3) derivatives suggest that the configuration of the ring C of morphine plays only a minor role in morphine-like analgesics to display an analgesic action. The conformation among the ring A and D and the nitrogen of morphine seem to be essential for the interaction of morphine-like analgesics with analgesic receptors (24). If the inference discussed above is reasonable, the second assumption could not be denied.

MT-45 has not a structural resemblance to any morphine-like analgesic having a partial structure of morphine except for Spa. Accordingly, if MT-45 is not a pharmacological analogue of Spa, MT-45 belongs to a new type of compounds with morphine-like analgesic activity without the structural resemblance. This suggests that the third assumption is more reasonable, as the inversion of basic anilide analgesics in the enantiomeric potency ratio has been rationalized as being reflective of different modes of interaction of narcotics with receptors (25–29).

The analgesic potency ratio (the more active form/the racemic form) less than 2 means that the less active enantiomer must be active in its own right and/or potentiate the action of the more potent enantiomer (3). The analgesic potency ratios (the S-isomer/the racemic form) of MT-45 were 1.61, 1.97 and 1.14 in mice (s.c.) and 1.23 and 1.00 in rats (s.c.), and the S/R ratios were 25.1, 42.1 and 18.3 in mice and 61.6 and more than 13.9 in rats. These results suggest the possibility that the R-isomer potentiates the analgesic activity of the S-isomer, though there is a variation among the assay methods. Such a potentiating tendency of the R-isomer to the S-isomer was observed on the gastrointestinal propulsion, pupil size (mice) and body temperature (Fig. 3–5).

Green (30) has reported that the ratio of the analgesic dose to the dose preventing transport of a charcoal meal in rats was about the same for seven well known narcotics. Janssen and Jageneau (31) have reported that they found a parallelism, but no obvious quantitative correlation of the inhibiting activity of the gastrointestinal propulsion and the analgesic activity in mice and rats, while a significant correlation was found in mice with the analgesic and the mydriatic action with many analgesically active compounds. On the other hand, morphine induces hyperglycemia in cats (32), dogs (33) and rabbits (34), and a relationship between the analgesic activity and the hyperglycemic activity of known narcotics in rabbits has been reported by Ishikawa (34). The R-isomer showed no or very weak effects on the pupil size in mice and rabbits, body temperature in rats and plasma glucose level in rabbits at doses of 10 to 30 mg/kg, s.c., while Spa, showing analgesic activity as potent as the R-isomer, showed a consistent effect at 30 mg/kg, s.c. Furthermore, the local anesthetic activity of the R-isomer was about 33 and 67 times as potent as that of Spa and morphine, respectively. These results may suggest that the mode of action of the R-isomer is partly different from that of Spa.

From the results described above, it may be concluded that the cyclohexylpiperazine moiety of MT-45 plays a significant role to exhibit analgesic activity, and that MT-45 belongs to a new series of compounds having potent analgesic properties.

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References

1. PORTOGHESE, P. S. *J. pharm. Sci.* **55**, 865 (1966).
2. KANEMATSU, K. *Kagaku No Ryoiki* **17**, 966 (1963).
3. CASY, A. F. *Medicinal Chemistry*, Part I (A. Burger, Ed.), pp. 81, (Wiley-Interscience, New York-London, 1970).
4. NATSUKA, K., NAKAMURA, H., UNO, H. and UMEMOTO, S. *J. med. Chem.*, **18**, 1240 (1975).
5. FUJIMURA, H., KAWAI, K., OHHATA, K. and SHIBATA, S. *Folia pharmacol. jap.* **56**, 522 (1960).
6. FUJIMURA, H. and KAWAI, K. *Folia pharmacol. jap.* **56**, 514 (1960).
7. NAKAZAKI, M., MITA, I. and TOSHIOKA, N. *Bull. Chem. Soc. Japan*, **36**, 161 (1963).
8. D'AMOUR, F. E. and SMITH, D. L. *J. Pharmacol. exp. Ther.* **72**, 74 (1941).
9. NAKAMURA, H., KADOKAWA, T., NAKATSUJI, K. and NAKAMURA, K. *Arzneimittelforsch.* **20**, 1032 (1970).
10. NILSEN, P. L. *Acta pharmacol.* **18**, 10 (1961).
11. SIEGMUND, E., CADMUS, R. and LU, G. *Proc. Soc. exp. Biol.*, N.Y., **95**, 792 (1957).
12. LITCHFIELD, J. T. JR. and WILCOXON, F. *J. Pharmacol. exp. Ther.* **96**, 99 (1949).
13. HERRMAN, J. B. *J. Pharmacol. exp. Ther.* **76**, 309 (1942).
14. DITTRICH, W. *Arch. exp. Path. Pharmakol.* **168**, 307 (1932).
15. SUDA, M. *Folia pharmacol. jap.* **53**, 614 (1957).
16. TAKAGI, K., FUKUDA, H., WATANABE, M. and SATO, M. *Yakugaku Zasshi* **80**, 1506 (1957).
17. GOTO, K., YAMASAKI, H., YAMAMOTO, I. and OHNO, H. *Proc. Japan Acad.* **33**, 660 (1957).
18. KALVODA, J., BUCHSCHACHER, P. and JEGER, O. *Helv. chim. Acta* **38**, 1847 (1955).
19. CORRODI, H. and HARDEGGER, E. *Helv. chim. Acta* **38**, 2038 (1955).
20. BENSON, W. M., STEFKO, P. L. and RANDALL, L. O. *J. Pharmacol. exp. Ther.* **109**, 189 (1953).
21. HELLERBACH, J., SCHNIDER, O., BESENDORF, H. and PELLMONT, B. *Synthetic Analgesics*, Part II A, (Pergamon Press, New York, 1966).
22. NAKAZAKI, M. *Chem. Ind.*, Lond., 1577 (1962).
23. GATES, M. and WEBB, W. G. *J. amer. chem. Soc.* **80**, 1186 (1958).
24. BECKETT, A. H. and CASY, A. F. *J. Pharm. Pharmacol.* **6**, 986 (1954).
25. WRIGHT, W. B. and HARDY, R. A. *J. med. Chem.* **6**, 128 (1963).
26. PORTOGHESE, P. S. *J. med. Chem.* **8**, 147 (1965).
27. PORTOGHESE, P. S. *J. med. Chem.* **8**, 609 (1965).
28. CASY, A. F. and HASSAN, M. M. A. *J. Pharm. Pharmacol.* **19**, 17 (1967).
29. PORTOGHESE, P. S. *Annu. Rev. Pharmacol.* **10**, 51 (1970).
30. GREEN, A. F. *Brit. J. Pharmacol.* **14**, 26 (1959).

31. JANSSEN, P. A. J. and JAGENEAU, A. H. *J. Pharm. Pharmacol.* **9**, 381 (1957).
32. BORISON, H. L., FISHBURN, B. R., BHIDE, N. K. and MCCARTY, L. E. *J. Pharmacol. exp. Ther.* **138**, 229 (1962).
33. VASSALLE, M. *Fed. Proc.* **19**, 120 (1960).
34. ISHIKAWA, M. *Folia pharmacol. jap.* **52**, 646 (1956).

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