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Analgesic and other pharmacological activities of a new narcotic antagonist analgesic (—)-1-(3-methyl-2-butenyl)-4-[2-(3-hydroxyphenyl)-1-phenylethyl]-piperazine and its enantiomorph in experimental animals

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Of 1-cyclohexyl-4-[2-(3-hydroxyphenyl)-1-phenylethyl]piperazine (I) and its 1-(3-methyl-2-butenyl) derivative (II), the *S*(+)-isomers were analgesically more active than either their *R*(−)-isomers or their racemates, having 15 to 44 times the potency of morphine in mice and rats. *R*(−)-I had comparable analgesic activity to morphine *R*(−)-II to pentazocine in mice, rats and dogs and they were nearly equipotent with pentazocine in reversing some actions of morphine. The *S*(+)-isomers and racemates lacked this action. *R*(−)-II required about 10 times more naloxone to reverse its analgesic activity than was needed to antagonise the *S*(+)-isomers, morphine and pentazocine. The *S*(+)-isomers and racemates produce a typical Straub tail reaction and increased spontaneous locomotor activity in mice, but the *R*(−)-isomers did not. *R*(−)-II had no significant physical dependence liability in mice, rats and monkeys. From these results, it is suggested that the compounds show an uncommon stereoselectivity in comparison with morphine and its surrogates, and that *R*(−)-II is worth investigating further as a narcotic antagonist analgesic.

Morphine-like analgesics have a high stereospecificity in many actions (Beckett & Casy 1954; Bentley et al 1971). There is a structural resemblance by virtue of their tyramine moiety (Fig. 1) being important for the opiate-receptor interaction (Beckett & Casy 1954; Bentley et al 1971; Bentley & Lewis 1972; Feinberg et al 1976; Bella 1975; Galt 1977; Kolb 1978). The structural similarity of met^5-enkephalin to morphine has been pointed out, and the tyramine moiety has been also required for analgesic activity (Horn & Rodgers 1977; Hughes & Kosterlitz 1977; Schiller et al 1977; Frederickson 1977). However, the α-carbon of the tyramine moiety of met^5-enkephalin shows the *S*-configuration (Maryanoff & Zelesko 1978) which is opposite to morphine and its analogues (Portoghese 1966; May & Sargent 1965), and its *R*-enantiomer is inactive (Coy et al 1976). Nakamura & Shimizu (1976) and Natsuka et al (1975) have reported that the *S*(+)-enantiomer of (±)-1-cyclohexyl-4-(1,2-diphenylethyl)piperazine (MT-45) has 20 to 30 times the analgesic potency of the *R*(−)-enantiomer, which itself has pharmacological activities different from morphine. Recently, it has been strongly suggested that the opiate receptors in the central nervous system are not a homogeneous population (Martin et al 1976; Gilbert & Martin 1976; Lord et al 1977; Bella et al 1978), and that some effects of morphine and its analogues may be mediated by interaction with separate receptors (Smits & Takemori 1970; Smith & Crofford 1975; McGilliard et al 1976; Jacquet 1978). From these findings, our attention was turned to the less active isomers of MT-45 derivatives with the object of dissociating analgesic activity from dependence liability as a result of receptor interactions different from those of morphine and its surrogates. We found that a stereoselectivity among compounds I (the *m*-hydroxyl derivative of MT-45, Natsuka et al 1978) and II (Fig. 1, Nishimura et al 1978) was different from that of the morphine-like analgesics and that their *R*(−)-isomers showed as potent analgesic activity as morphine or pentazocine but no significant physical dependence liability in animals. This paper presents pharmacological activities of the enantiomorphs of compounds I and II in experimental animals.

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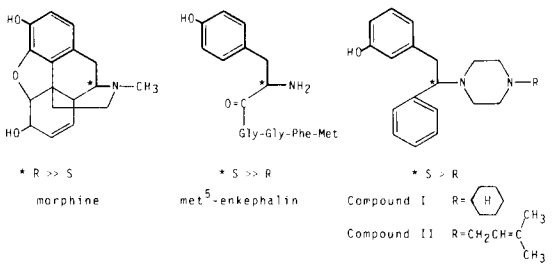

FIG. 1. Chemical structure of 1-(3-methyl-2-butenyl)-4-[2-(3-hydroxyphenyl)-1-phenylethyl]piperazine (compound II) and the 1-cyclohexyl derivative (compound I) in comparison with morphine and met^5-enkephalin.

MATERIALS AND METHODS

Analgesic assay

A tail flick response was induced by heat radiation on the blackened tail of male mice (9–12 g) of ddN strain using an apparatus and procedure as described by Nakamura & Shimizu (1976). Mice showing a response time of 4 to 6 s were used. After subcutaneous drug administration the response time was measured 6 times at 30 min intervals with an arbitrary cutoff time of 15 s. When the response time was 10 s or more, the drug was considered to be effective. Ten to 15 mice were used for each dose.

The effect of the drugs on pressure (Haffner 1929) was assessed in male rats (100–150 g) of Wistar strain using the apparatus and procedure of Nakamura & Shimizu (1976). The threshold was measured as mm (1 mm = 12·5 g pressure) with an arbitrary cutoff pressure of 50 mm at 15 to 30 min intervals for 2 h after subcutaneous drug administration. When the threshold was 40 mm or more, the drug was considered to be effective. Ten to 15 rats were used for each dose.

Chewing, licking or twitching movements induced by stimulation of tooth pulp of 30 Hz for 5 ms for 3 s through the platinum electrodes implanted chronically in conscious dogs, were measured at 5 to 30 min intervals for 2 h after subcutaneous drug administration (Mitchell 1964; Neat & Peacock 1971; Nakamura et al 1979). Four mongrel dogs of either sex, 8–12 kg, were used for each dose.

A response to bradykinin was induced by injecting 1 μg into the splenic artery toward the spleen in dogs under light anaesthesia (Guzman et al 1964; Hashimoto et al 1964; Nakamura et al 1979). Only those animals showing an increase of 20 to 40 mmHg in systemic blood pressure following injection were used. The blood pressure was measured before and 5, 15 and 30 min after i.v. drug administration. When the response decreased by more than 50% compared with the pre-drug value, the drug was considered to be effective. Three or 4 male mongrels or beagles, 8–12 kg, were used for each dose.

Acetic acid writhing was induced by intraperitoneal injection of 1 ml of a 1% acetic acid aqueous solution in male rats (90–120 g) of Wistar strain (Niemegeers et al 1975). Fifteen min later, each drug was administered s.c. to those animals showing the writhing syndrome, and the number of writhes was counted for 20 min beginning from 60 min after acetic acid challenge. When the number of writhes decreased by more than 50% compared with the vehicle control group, the drug was considered to be effective. Ten rats were used for each dose.

Phenylquinone writhing was induced by phenylquinone (0·03% in 5% ethanol aqueous solution), 10 ml kg^{-1}, i.p., in female mice (18–22 g) of ddN strain (Siegmund et al 1957; Nakamura & Shimizu 1976). The number of writhes was counted for 15 min beginning 5 min after phenylquinone challenge. Each drug was administered s.c. 30 min before phenylquinone. When number of writhes decreased by more than 50% compared with the vehicle control group, the drug was considered to be effective. Ten to 15 mice were used for each dose.

Narcotic antagonist assay

To determine antimorphine activity, three methods were used in mice or monkeys. In the tail flick test, the antagonist ED50 value was calculated from the number of positive mice showing the response time of less than 10 s at 30 or 60 min after a single subcutaneous injection of 5 mg kg^{-1} of morphine hydrochloride, that was effective (14 to 15 s) in prolonging the response time to thermal stimulus in 95% of animals. Each drug was administered subcutaneously just before morphine injection. Ten to 15 mice were used for each dose.

In the mouse Straub tail test (Shemano & Wendel 1964), the antagonist ED50 value was calculated from the number of positive animals showing no or weak (less than 90 degrees) tail elevation for 5 min beginning from 1 min after a single intravenous injection of 10 mg kg^{-1} of morphine hydrochloride that was effective in producing a typical tail erection (more than 90 degrees) in 95% of animals. Each drug was administered subcutaneously 15 min before morphine injection. Ten to 15 male mice of STDddY strain, 20–26 g, were used for each dose.

In morphine-dependent rhesus monkeys, which were given 9 mg kg^{-1} s.c. of morphine hydrochloride

twice daily at 0900 and 1700 h, we tested whether morphine withdrawal signs were precipitated by a single administration of each drug. Three mg kg^{-1} s.c. of morphine hydrochloride was administered 25 h after morphine withdrawal (1000 h), and 2 h later each drug was administered subcutaneously to the monkeys. Four monkeys were used for each dose.

Physical dependence assay

Straub tail index. Each drug was rapidly administered through the tail vein of male mice (18–22 g) of ddN strain and the erection of the tail to more than 90 degrees was observed for 20 min after each drug administration (Shemano & Wendel 1964). Ten mice were used for each dose.

Nalorphine-precipitated jumping test. Male mice (19–23 g) of ddN strain received 7 subcutaneous administrations of each drug in increasing doses of 8, 16, 25, 50, 100, 100 and 100 mg kg^{-1} for 2 days; five doses were given on the first day at 0900, 1000, 1100, 1300 and 1500 h, and two were given on the second day at 0900 and 1100 h. Two h after the last dose, the animals received a single intraperitoneal injection of 50 mg kg^{-1} of nalorphine hydrochloride, and jumping behaviour and other withdrawal signs were observed for 30 min in a separate cylinder (40 cm high and 15 cm in diameter) (Saelens et al 1971; Nakamura et al 1973). Ten to 30 mice were used for each dose.

Two doses substitution test in morphine-dependent rats. Male rats (200–250 g) of Wistar strain were used. Morphine-dependent rats receiving morphine hydrochloride s.c. with a maintenance dose of 100 mg kg^{-1} twice daily (0900 and 1700 h) according to Nakamura et al (1978), were given each drug s.c. morning and evening for one day in place of doses of morphine. The number of wet dog shakes and writhing, locomotor activity, and other withdrawal signs was measured 1·5 and 4 h after the morning administration for each 15 min; the rectal temperature was measured at 1·5 and 6 h; the body weight was measured at 8 and 24 h (Nakamura et al 1975; Martin 1963; Buckett 1964). Eight rats were used for each dose.

Dependence producing test. Male rats (150–180 g) of Wistar strain were given each drug twice daily s.c. at 0900 and 1700 h for more than 7 weeks (Hosoya & Otobe 1958). The dose was increased weekly until the maximum tolerated dose or the maintenance dose was reached; the maximum tolerated dose of *R*(−)-I, *R*(−)-II and pentazocine was 20 mg kg^{-1} twice daily. Withdrawal signs precipitated by a cessation of drug administration or by a single injection of 10 mg kg^{-1} s.c. of levallorphan tartrate were observed for 24 or 72 h; body weight loss, wet dog shakes, writhing, diarrhoea, teeth chattering, irritability, decreased locomotor activity, decreased body temperature were used as withdrawal signs (Nakamura et al 1978). Ten to 15 rats were used for each dose.

A single suppression test in morphine-dependent monkeys. Morphine physical dependence was induced in rhesus monkeys (2·2–2·6 kg) by subcutaneous injections of morphine hydrochloride twice daily at 0900 and 1700 h for more than 2 months (Seevers 1936; Yanagita 1973; Crossland & Turnbull 1977). The initial dose of 6 mg kg^{-1} twice daily was increased to 9 mg kg^{-1} twice daily (maintenance dose) 6 weeks later. Physical dependence was indicated by the withdrawal signs which appeared gradually over 48 h following morphine withdrawal; these signs included restlessness, shivering, continual calling and crying, limb biting, tremor, muscle twitching and rigidity, peculiar attitudes, lying on the side with eyes closed and holding the abdomen. Each drug was administered subcutaneously 25 h after morphine withdrawal when withdrawal signs were usually of intermediate intensity. The observer, who was unaware of which drug had been administered, noted the withdrawal signs for 5 h after drug administration. Four monkeys were used for each dose.

Spontaneous locomotor activity

Male mice of STDddY strain, 22–30 g, were used. Five mice were placed together in a cage (23 × 39 × 30 cm) on the Animex Activity Meter immediately after a single subcutaneous injection of each drug, and the level of spontaneous locomotor activity was recorded consecutively for 4 h at 10 min intervals (Nakamura & Shimizu 1977a). Six to eight groups of mice were used for each dose.

Statistical analysis

Analgesic and narcotic antagonist ED50 values and 95% confidence limits were calculated from the effective rates of 4 to 6 doses according to the method of Litchfield & Wilcoxon (1949). Analgesic potency ratio and 95% confidence limits were calculated according to the parallel line assay method (Finney 1952).

Drugs

Drugs used were as follows: morphine hydrochloride, codeine phosphate, pethidine hydro-

chloride, tramadol hydrochloride, nalorphine hydrochloride, levallorphan tartrate, naloxone hydrochloride, pentazocine, 1-cyclohexyl-4-[2-(3-hydroxyphenyl)-1-phenylethyl]piperazine (I) dihydrochloride except (±)-I dihydrobromide, and 1-(3-methyl-2-butenyl)-4-[2-(3-hydroxyphenyl)-1-phenylethyl]-piperazine (II) dihydrochloride. Melting points (uncorrected) taken in a capillary and optical rotations (in MeOH) of the compounds were as follows. *R*(−)-I·2HCl: m.p. 283–284 °C; $[\alpha]_D^{28}$ −51·6° (c, 0·55), *S*(+)-I·2HCl: m.p. 283–284 °C; $[\alpha]_D^{27}$ +51·5° (c, 0·55), *R*(−)-II·2HCl: m.p. 228·5–230 °C (dec.); $[\alpha]_D^{27}$ −60·3° (c, 2·00), *S*(+)-II·2HCl: m.p. 228·5–230 °C (dec.); $[\alpha]_D^{28}$ +60·2° (c, 2·00), (±)-II·2HCl: m.p. 241–242 °C (dec.) and (±)-I·2HBr (Natsuka et al 1978). All compounds were analysed for C, H, N and Cl; analytical results were within ±0·3% of the theoretical values. The absolute configulation of these optical isomers was determined by optical rotatory dispersion measurements.

Each dose is expressed as the salt form of the drugs and compounds.

RESULTS

Analgesic activity

The enantiomorphs were tested for analgesic activity against various nociceptive stimuli in mice, rats and dogs (Tables 1 and 2). The *S*(+)-isomers of I and II were more active than the *R*(−)-isomers and racemates when given s.c., and their analgesic potencies were 15 to 44 times that of morphine in the tail flick test. Of the *R*(−)-isomers *R*(−)-I was nearly equipotent with morphine and *R*(−)-II with pentazocine, in mice, rats and dogs. The *R*(−)-isomers like pentazocine, showed weaker activity in the tail flick test than in the other tests. The potency ratios of *S*(+)-II to racemate-II were significantly ($P = 0·05$) larger than 2·0 in thermal and pressure tests, though the ratios of compound I were about 1·8 (Table 1).

Table 1. Analgesic activity of enantiomorphs of compounds I and II in comparison with narcotic agonists and antagonists in mice and rats.

	Analgesic ED50 (mg kg^{-1}, s.c.) against various nociceptive stimuli		
	Pressure* rats	Tail flick† mice	Phenylquinone§ mice
I			
(±)-I 2HBr	0·059 (0·036–0·097)	0·126 (0·076–0·208)	0·0037 (0·0014–0·0102)
S(+)-I 2HCl	0·027 (0·019–0·038)	0·054 (0·039–0·075)	0·0030 (0·0012–0·0080)
R(—)-I 2HCl	0·348 (0·222–0·544)	4·24 (3·32 –5·81)	0·0275 (0·0084–0·0896)
II			
(±)-II 2HCl	0·101 (0·084–0·122)	0·426 (0·361–0·504)	0·0197 (0·0100–0·0391)
S(+)-II 2HCl	0·031 (0·025–0·038)	0·162 (0·127–0·207)	0·0055 (0·0018–0·0168)
R(—)-II 2HCl	2·99 (2·07 –4·31)	41·1 (25·3 –66·9)	1·87 (1·08 –3·25)
Morphine HCl	1·17 (0·65 –2·28)	2·39 (1·78 –3·20)	0·58 (0·43 –0·77)
Codeine H_3PO_4	16·0 (9·93 –25·7)	28·1 (19·9 –39·8)	3·55 (1·42 –8·86)
Tramadol HCl	18·0 (15·5 –21·0)	24·0 (15·1 –38·0)	3·16 (1·82 –5·49)
Pentazocine	13·2 (6·23 –28·1)	>160	1·87 (0·826 –4·07)
Nalorphine HCl	>80	> 80	0·305 (0·087 –1·07)
Naloxone HCl	>80	> 80	>80

	Analgesic potency ratio of *S*(+)-isomer/racemate	
	Pressure (rats)*	Tail flick (mice)†
Compound I	1·80 (0·94–3·86) n = 69	1·89 (1·23–3·01) n = 105
Compound II	3·32 (2·36–4·66) n = 80	2·91 (2·21–4·00) n = 120

Parentheses represent 95% confidence limits. Analgesic potency ratio was calculated according to the parallel line assay method (Finney 1952). Only for the potency ratio, (±)-I dihydrobromide was calculated in terms of hydrochloride salt.

* Pressing the tail. † Radiating heat light on the tail. § Phenylquinone writhing.

Narcotic antagonist activity

R(−)-II was equipotent with pentazocine in reversing the analgesic activity of morphine in the tail flick test, but the *S*(+)-isomers and racemates were inactive (Table 3). *R*(−)-I reversed the activity

Table 2. Analgesic activity of *R*(—)-isomers in comparison with pentazocine and morphine in rats and dogs.

	Analgesic ED50 (mg kg^{-1}, s.c.) against		
	Bradykinin stimulus		Electrical stimulus§
	rats*	dogs†	dogs
R(−)-I 2HCl	0·10 ca.		
R(−)-II 2HCl	1·17 (0·73–1·90)	4·24 (1·80–9·99)	4·1 (2·3–7·3)
Pentazocine	2·45 (1·96–3·07)	5·29 (1·80–15·6)	3·6 (2·4–5·5)
Morphine HCl	0·20 (0·12–0·33)	1·38 (0·96–1·99)	0·8 (0·5–1·5)

Parentheses represent 95% confidence limits.
* Acetic acid writhing.
† Bradykinin injection into the splenic artery. Drugs were given intravenously.
§ Electrical stimulation of tooth pulp.

only at low doses (up to 8 mg kg^{-1}), since its agonist action appeared at more than 16 mg kg^{-1}. *R*(−)-II (4–16 mg kg^{-1} s.c.) reversed the analgesic activity of pethidine hydrochloride (10 mg kg^{-1} s.c.) in tail flick and Straub tail test (Table 3) and increased spontaneous locomotor activity of morphine in mice. Furthermore, *R*(−)-II and pentazocine when given 8 mg kg^{-1} s.c. precipitated withdrawal signs in morphine-dependent rhesus monkeys. Consequently, it is suggested that the *R*(−)-isomers have narcotic antagonist activity at least equivalent to pentazocine.

Naloxone antagonism of analgesic activity of R(−)-II

Naloxone hydrochloride reversed the analgesic activity of the *S*(+)-isomers, morphine and pentazocine at doses of 0·01 mg kg^{-1} s.c. or more and 0·04 mg kg^{-1} s.c. or more in the acetic acid and phenylquinone writhing tests, respectively. On the contrary, the activity of *R*(−)-II was reversed significantly only by 0·1 mg kg^{-1} s.c. and 0·4 mg kg^{-1} s.c. of naloxone hydrochloride in the two tests, respectively (Fig. 2). Thus, *R*(−)-II requires about 10 times more naloxone to reverse its analgesic action than is needed to antagonize morphine and pentazocine.

Table 3. Narcotic antagonist activity of enantiomorphs of compounds I and II against morphine-induced analgesia and tail erection in mice.

	Antimorphine ED50 (95% confidence limits) in mg kg^{-1}, s.c.	
	Analgesia in tail flick test	Straub tail phenomenon
I		
(±)-I 2HBr	NA*	
S(+)-I 2HCl	NA	
R(−)-I 2HCl	4·76 (1·61 –14.1) n = 75	3·04 (1·74 –5.31) n = 36
II		
(±)-II 2HCl	NA	
S(+)-II 2HCl	NA (or slight)	
R(−)-II 2HCl	3·54 (1·52 –8·20) n = 50	6.15 (3·63 –10·4) n = 60
Pentazocine	3·79 (1·47 –9·74) n = 60	7·16 (4·37 –11·7) n = 50
Nalorphine HCl	0·082 (0·040–0·169) n = 50	0·042 (0·028–0·062) n = 86
Naloxone HCl	0·016 (0·008–0·031) n = 40	0·010 (0·005–0·020) n = 78

* NA no antimorphine activity.

Physical dependence liability

In all the tests shown in Table 4, *R*(−)-II did not show significant morphine-like physical dependence liability. Codeine showed a definite morphine-like activity in all the tests, and pentazocine showed slight Straub tail reaction in mice and slight substitution activity for morphine in morphine-dependent

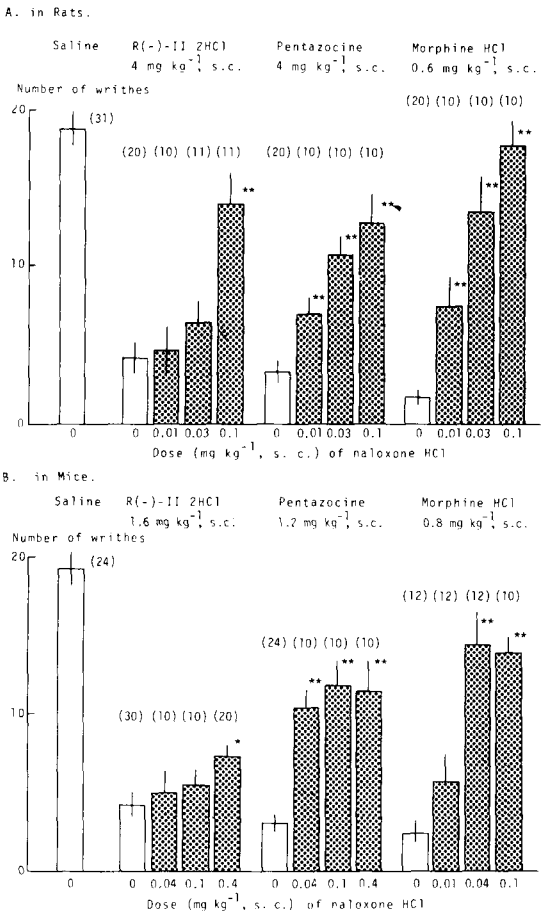

FIG. 2. Naloxone antagonism of analgesic activity of *R*(−)-II, pentazocine and morphine in rats and mice. A. Rats were given i.p. 1 ml of a 1% acetic acid aqueous solution, and 15 min later each drug with naloxone or with saline was administered subcutaneously to the rats. The number of writhings was counted for 20 min beginning from 60 min after acetic acid challenge. B. Mice were given intraperitoneally 10 ml kg^{-1} of a 0·03% phenylquinone solution 5 min after subcutaneous administration of each drug with naloxone or with saline. The number of writhings was counted for 15 min beginning from 5 min after phenylquinone challenge. Vertical bars represent the s.e.m. ( ) number of animals used. * $0{\cdot}01 < P < 0{\cdot}05$ and ** $P < 0{\cdot}01$ significantly different from each group without naloxone.

Table 4. Physical dependence liability of *R*(—)-I and *R*(—)-II in comparison with narcotic agonists and antagonist in mice, rats and monkeys.

	Straub* tail index mice	Nalorphine-** precipitated jumping mice JD50 mg kg^{-1}	Two doses† substitution for morphine rats (mg kg^{-1})	Dependence‡ production by chronic treatment rats	Single dose§ suppression of morphine withdrawal monkeys (mg kg^{-1})
R(—)-I 2HCl	slight tail elevation	>203	no	slight	no (up to 8)
R(—)-II 2HCl	no tail elevation	>399	no	no	no (up to 16)
Pentazocine	slight tail elevation	>325	slight (50–100 × 2)	no	no (up to 16)
Tramadol HCl	3·0	399 ca.	middle (100 × 2)		no (up to 16)
Codeine H_3PO_4	8·1	325	complete (100 × 2)	severe	middle to complete (8)
Morphine HCl	62·8	20·3	complete (25 × 2)	severe	middle to complete (1–3)

Drugs were subcutaneously administered in the tests other than Straub tail index (i.v.).
* The ratio of LD50/Straub tail ED50.
** JD50 is a 50% jumping dose per 2 days.
† Capacity to substitute for morphine in morphine-dependent rats; drugs were given twice.
‡ Withdrawal signs were observed following abrupt withdrawal of drugs or levallorphan administration in rats receiving the subtoxic or maximum tolerated doses of drugs twice daily for more than 7 weeks.
§ Capacity to suppress withdrawal signs in morphine-dependent monkeys; the highest dose tested on both the *R*(—)-isomers was the highest dose not associated with severe toxic effects.

rats. *R*(−)-I showed a slight Straub tail reaction in mice and slight dependence-producing activity in rats receiving *R*(−)-I chronically at a subtoxic dose (30 mg kg^{-1} s.c. twice daily). The *S*(+)-isomers and racemates produced a typical Straub tail reaction and a nalorphine-precipitated jumping syndrome at lower doses than morphine in mice.

Spontaneous locomotor activity

Opioids having potent psychic dependency increase spontaneous locomotor activity in mice. The *S*(+)-isomers and racemates, like morphine, markedly increased locomotion in grouped mice, and pentazocine and tramadol increased it at high doses (Fig. 3). On the contrary, *R*(−)-I did not increase and *R*(−)-II decreased the locomotion.

DISCUSSION

The results show that the *S*(+)-isomers are the most active and with the racemate have only agonist activity while the *R*(−)-isomers have both agonist and antagonist actions. It is unusual that only the *R*(−)-isomers have narcotic antagonist activity, since narcotic antagonists generally have the same stereospecificity as the agonists (Martin 1967; Tullar et al 1967; Pircio et al 1976). If only one nitrogen atom in the molecule participates in opiate receptor binding, similar to morphine and nalorphine (Kolb 1978; Feinberg 1976), the antagonist activity should also be found in the *S*(+)-isomers and the racemates.

Some analgesics are considered to interact with the opiate receptors in a manner different from morphine (Portoghese 1965; Bella 1975; Galt 1977) and the presence of more than one morphine receptor has been postulated (Gilbert & Martin 1976; Martin et al 1976). Many narcotic analgesics produce a marked increase in spontaneous locomotor activity with a symbolic tail erection in mice. Nakamura & Shimizu (1977b) have reported that narcotic analgesics, and drugs having psychic dependency, increase spontaneous locomotor activity in grouped animals and that there is a rough relation between the extent of spontaneous locomotor activity and psychic dependency. But the *R*(−)-isomers did not increase locomotion in grouped mice and *R*(−)-II decreased it without the tail erection (Fig. 3). Also, *R*(−)-II's analgesic action was not easily reversed by naloxone (Fig. 2). Thus the pharmacological properties of *R*(−)-II are dissimilar from morphine, so it may be postulated that *R*(−)-II either interacts with opiate receptors in a manner different from morphine or interacts with a receptor different from the morphine receptor.

It has not been considered possible to dissociate morphine's analgesic action from its physical

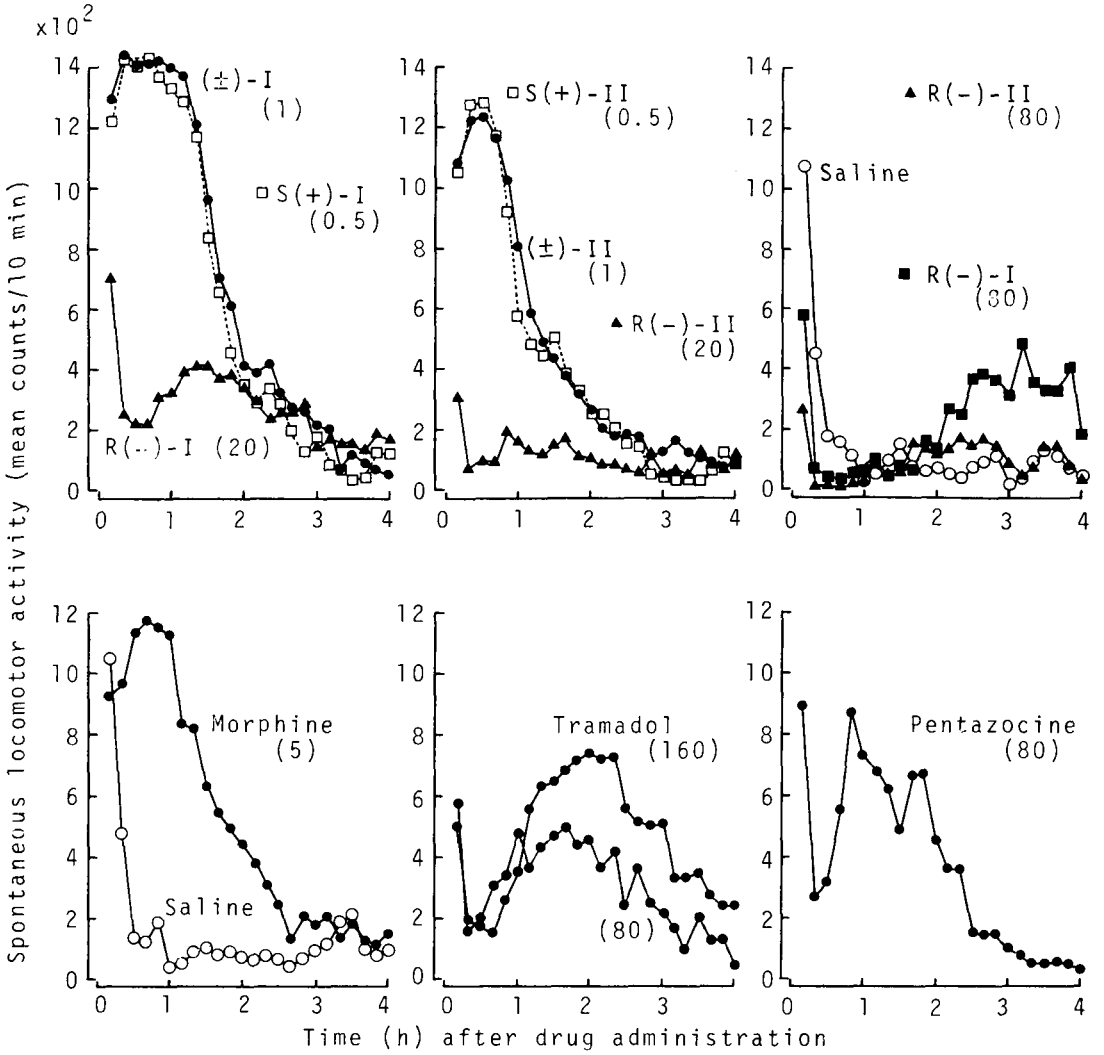

FIG. 3. Effects of enantiomorphs of compounds I and II on spontaneous locomotor activity in grouped mice. Five mice were placed together in a cage on the Animex Activity Meter after s. c. administration of drugs, and the level of locomotion was recorded consecutively for 4 h at intervals of 10 min. Each point represents the mean from six to eight groups of mice.
( ) dose in mg kg^{-1} as each salt form of compounds or drugs.

dependence liability, and most compounds with potent analgesic activity have shown a physical dependence liability similar to morphine; whether both the actions are mediated by interaction with the same receptor is unclear. However, the analgesic action of drugs like pentazocine and tramadol is relatively separated from their physical dependence liabilities. The analgesic action of morphine is prevented by reserpine pretreatment (Vogt 1954; Sigg et al 1958; Takagi et al 1964), though there is no evidence that physical dependence liability is affected by reserpine. From these findings and other pharmacological properties of morphine and its analogues, we have supposed that the analgesic receptor is different from the receptor (or site of action) producing physical dependency, though both of the receptors may occur close to one another and/or bear a close resemblance. The present results on the *R*(−)-isomers, which is supposed to cause receptor interactions different from morphine and its surrogates, seem to support our view.

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