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# (1,2-DIPHENYLETHYL) PIPERAZINES AS POTENT OPIATE-LIKE ANALGESICS; THE UNUSUAL RELATIONSHIPS BETWEEN STEREOSELECTIVITY AND AFFINITY TO OPIOID RECEPTOR

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## Summary

A series of novel diphenylethylpiperazines were synthesized, and analgesic activities and opioid receptor interactions were evaluated. Analgesic activity of S(+) enantiomer of 1-cyclohexyl analogues (I-C6) was as potent as morphine. This compound showed narcotic properties. Racemate of I-C6 demonstrated the most potent analgesic activities among the enantiomorphic pairs. The R(-) isomer and (-) spa,NN-dimethyl-1,2-diphenylethylamine, had mu-agonist like character. The S(+) isomer possessed high affinity for all types of the receptor, especially favorable for delta and kappa, in the defferent manner from opiate-like analgesics. It is conceivable that opioid receptor has various subsites, and this S(+) enantiomer alter the conformation of the receptor.

We previously reported that the chemical structure of R(-) NN-dimethyl 1,2-diphenylethylamine, (-) spa, is the essential configulation for morphine-like analgesic, with results of conformational analysis (1). Analgesic activity and the receptor affinity of (-) spa are approximately equipotent to those of codeine. By considering structural modification of (-) spa, a series of novel diphenylethylpiperazine derivatives were synthesized in our laboratories. These analgesic activities and the opioid receptor bindings were evaluated.

## Materials and Methods

The structures of these piperazines are shown in Fig. 1. $^{3}$H-Dyhydromorphine (DHM, 70Ci/mmol), $^{3}$H-D-Ala$^{2}$-D-Leu$^{5}$-enkephalin (DADLE, 27.4Ci/mmol) and $^{3}$H-ethylketocyclazocine (EKC, 21.8Ci/mmol) were obtained from NEN; $^{3}$H-naloxone (NLX, 45Ci/mmol) and $^{3}$H-diprenorphine (DPN, 6.1Ci/mmol) from Amersham.

Analgesic activity was determined by the Haffner method in which

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mechanical pain was induced by pressing the tail of male mice using forceps. In addition, the activity was evaluated in mice by acetic acid (AcOH) writhing test. Rapid filtration method, using crude synaptosomal membrane preparations from rat brain, were carried out the opioid receptor binding assay.

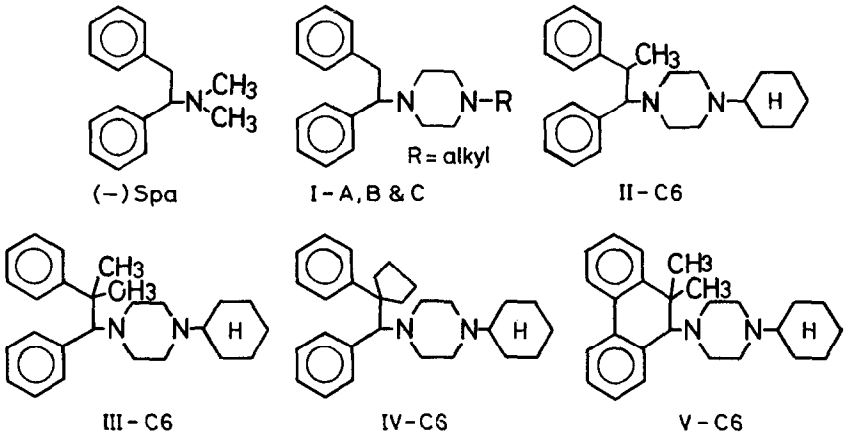


FIG. 1

Themical structure of (-) spa and 1-substituted 4-(1,2-diphenyl-alkyl) piperazine derivatives.
I-A group contains methyl(A1), ethyl(A2), n-propyl(A3), n-pentyl(A5) and n-hexyl(A6) derivatives. I-B group consists of isopropyl(B3), isobutyl(B4), isopentyl(B5) and isohexyl(B6) analogues. I-C group contains alylcyclic derivatives; cyclo-pentyl(C5), cyclohexyl(C6), cycloheptyl(C7) and cyclo-octyl(C8) derivatives.

## Results and Discussion

The results of analgesic tests for racemates of 1-alkyl piperazines (Group-I) are summarized in Table 1, and analgesic activities of optically active derivatives of alicyclic piperazines are presented in Table 2. All compounds of Group-I and II-C6 were found to be potent morphine-like analgesia. The most potent compound was 1-cyclohexyl analogues (I-C6, MT-45) and was in the potency range of morphine (2). In the case of 1-n-alkyl piperazines (I-A), R(-) enantiomers showed more potent activities like those of morphine-relate compounds In contrast, configuration-activity relationships of 1-alicyclic derivatives were reversed, compared with those of opiates. The activities of S(+) isomers were more potent than those of R(-) isomers. Racemate of I-C6 demonstrated the most potent analgesic activity which was about 4 times more potent than that of morphine (3). Analgesia due to S(+) isomer of I-C6 was accompanied with the Straub tail phenomenon.

The relative affinities for opioid receptor were evaluated by the inhibitory binding assay using DHM, NLX, DADLE and EKC. The results of 1-cyclohexyl derivatives (I-C6) were presented in Table 3. I-C6(s) had high affinities for all types of the receptor, and S(+) isomer of I-C6 was the most active of all isomers. This compound posessed high affinities for the binding sites of DADLE and EKC, and lower affinity for the site of DHM. Hill's coefficients from the displacement of all ligands by S(+) isomer of I-C6 were nearly 0.5, indicating weak selectivity for the receptor and significant conformational change of

TABLE I

Analgesic activities of 1-substituted 4-(1,2-diphenylethyl) piperazine derivatives in mice.

| | R | ED 50 (95% C.L.) mg/kg, s.c. | |
|---|---|---|---|
| | | Haffner test | AcOH writhing test |
| I-A1 | $CH_3$ | 50mg : 30% | 10.3 (7.6-19.2) |
| I-A2 | $C_2H_5$ | 37.0 (24.0-40.3) | 7.0 (5.3-9.24) |
| I-A3 | $C_3H_7$ | 10.3 (8.9-12.0) | 6.2 (4.6-8.4) |
| I-A4 | $C_4H_9$ | 5.4 (3.6-8.2) | 6.0 (4.4-8.2) |
| I-A5 | $C_5H_{11}$ | 15.0 (10.6-21.2) | 4.3 (3.5-5.3) |
| I-A6 | $C_6H_{13}$ | 50mg : 10% | 27.0 (23.3-31.0) |
| I-B3 | iso-$C_3H_7$ | 17.5 (13.0-23.6) | 13.7 (9.8-19.2) |
| I-B5 | iso-$C_5H_{11}$ | 2.0 (0.65-2.58) | 1.7 (1.20-2.28) |
| I-B6 | iso-$C_6H_{13}$ | 38.0 (26.4-54.7) | 19.5 (13.4-28.5) |
| I-C5 | cyclo-$C_5H_9$ | 13.5 (11.5-15.8) | 9.4 (7.5-11.8) |
| I-C6 | cyclo-$C_6H_{11}$ | 1.7 (1.2-2.6) | 0.64 (0.44-0.93) |
| I-C7 | cyclo-$C_7H_{13}$ | 13.2 (10.3-16.2) | 2.0 (1.6-2.5) |
| I-C8 | cyclo-$C_8H_{15}$ | 16.0 (12.6-21.3) | 18.1 (14.4-22.5) |
| II-C6 | | 2.8 (2.0-3.9) | 1.15 (0.9-1.5) |
| III-C6 | | 50mg : 45% | 8.0 (6.0-10.6) |
| IV-C6 | | 50mg : 20% | 50mg : 25% |
| V-C6 | | 50mg : 20% | 13.0 (10.0-17.2) |
| (-) Spa | | 19.0 (14.3-25.3) | 6.0 (4.4-8.1) |
| Codeine | | 23.9 (13.0-44.0) | 5.5 (4.6-6.6) |
| Morphine | | 5.9 (5.6-6.3) | 0.47 (0.31-0.71) |

TABLE II

Analgesic activities of optically active 1-alicyclic-4-(1,2-diphenylethyl) piperazine derivatives in mice.

| | Configuration | ED 50 (95% C.L.) mg/kg, s.c. | |
|---|---|---|---|
| | | Haffner test | AcOH writhing test |
| I-C5 | S(+) | 15.0 (8.8-25.5) | 6.3 (5.0-7.9) |
| | R(-) | 30.0 (18.7-48.0) | 14.1 (12.4-16.1) |
| I-C6 | S(+) | 4.3 (3.75-4.95) | 0.4 (0.29-0.55) |
| | R(-) | 50.0 (37.9-66.0) | 1.0 (0.68-1.48) |
| I-C7 | S(+) | 6.6 (5.4-8.1) | 1.6 (1.5-1.7) |
| | R(-) | 50mg : 20% | 16.0 (11.0-23.0) |
| I-C8 | S(+) | 4.4 (3.2-6.0) | 1.05 (0.8-1.5) |
| | R(-) | 50mg : 30% | 12.0 (9.0-16.0) |

the binding site(s) of the opioid receptor.

(-) Spa and R(-) isomer of I-C6 may be interacting with the receptor in same mode of morphine. The binding sites responsible for the binding of morphine-relate compounds and of S(+) isomer of I-C6 may differ with respect to their

recognition properties.

TABLE III

Relative affinities of 1-cyclohexyl-4-(1,2-diphenylethyl) piperazine for the stereospecific binding sites of various tritiated opioid ligands in rat brain homogenates.

| | IC 50, nM (Hill's coefficient) | | | |
|---|---|---|---|---|
| | DHM | NLX | DADLE | EKC |
| S(+) | 736 | 143 | 70.6 | 78.0 |
| | (0.54) | (0.56) | (0.35) | (0.53) |
| R(-) | 1610 | 1210 | 614 | 791 |
| | (1.09) | (1.21) | (0.46) | (0.54) |
| Racemate | 644 | 743 | 156 | 176 |
| | (0.75) | (0.78) | (0.39) | (0.51) |
| (-) Spa | 3082 | 3685 | 1110 | 4022 |
| | (1.06) | (0.71) | (0.63) | (0.88) |
| Morphine | 4.6 | 5.5 | 78.6 | 242 |
| | (0.93) | (0.94) | (0.41) | (0.55) |

There is a dynamic complementarity between drug and receptor. Stereoselectivity is in general a function of the potency or affinity of the more potent isomer. On the other hand, the drug must be able to produce particular changes in the conformation and charge distribution of the receptor, which are required for an adequate stimulus formation. It is conceivable that the expression of potent narcotic agonism of the S(+) isomers of 1-alicyclic-4-(1,2-diphenylethyl)piperazine derivatives is associated with the changes in the conformation of the receptor.

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