Communications to the Editor

Bimorphinans as Highly Selective, Potent κ Opioid Receptor Antagonists

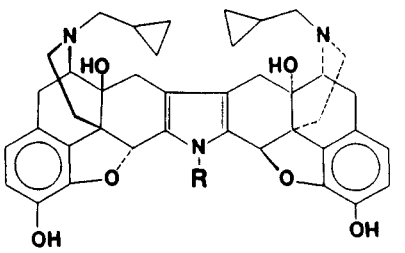
Sir:

The multiplicity[1] of opioid receptors and the numerous pharmacologic effects[2] mediated by opioid ligands have underscored the need for highly selective opioid antagonists as pharmacologic tools. The narcotic antagonists naloxone[3] and naltrexone[4] have been employed extensively as tools in opioid research, but their cross-recognition of different opioid receptor types (μ, δ, κ) is a serious limitation. Here we report on novel bimorphinans that possess high selectivity and potent antagonist activity at κ opioid receptors.

Our design of such ligands emanated from the "bivalent ligand" approach.[5] Bivalent ligands are molecules that contain two pharmacophores linked by a "spacer" whose constitution plays an important role in modulating selectivity and potency. This modulation may be related to the facility with which both pharmacophores bind simultaneously to vicinal recognition sites that are either identical or homologous. A key feature of this model is that each type of opioid receptor is located on dimeric or oligomeric subunits whose supramolecular organization contains a unique array of recognition sites that add an additional recognition pattern. Thus, the opioid recognition sites of each receptor type are postulated to be organized differently with respect to their mutual proximity and orientation.

Since we had observed that very short spacers increase κ opioid receptor selectivity of opioid antagonist bivalent ligands and that conformational factors also play a role in this process,[6,7] we have synthesized bivalent ligands (**1a**, **1b**) that contain two naltrexone-derived pharmacophores connected through a C-ring-fused pyrrole spacer. The position of this fusion rigidly fixes the relative orientation of the two pharmacophores.

Bimorphinans **1a** and **1b** were synthesized by heating the HCl salts of naltrexone (**2**) and the appropriate hydrazine ($RNHNH_2$; R = H, Me) under conditions similar to that reported for the Piloty–Robinson synthesis.[8,9] The



1a, R = H

1b, R = CH_3

structure and stereochemistry of the bimorphinans were confirmed by NMR and FAB-MS.[10]

The selectivities of **1a** and **1b** were evaluated in the guinea pig ileal longitudinal muscle[11] (GPI) and mouse vas deferens[12] (MVD) preparations (Table I). In the GPI, the bimorphinans behaved as weak antagonists of morphine (a μ-selective agonist), but they were highly potent in reversing the agonist effect of ethylketazocine (κ-selective agonist). The δ-selective agonist [D-Ala^2,D-Leu^5]enkephalin (DADLE) was weakly antagonized in the MVD. This was characterized by a parallel displacement of the agonist dose–response curves to higher concentration in the presence of the antagonists. The data clearly show the high κ opioid receptor selectivities of these bimorphinans. Moreover, the selectivity profiles differ remarkably from the standard opioid antagonist naltrexone (**2**), which prefers μ receptors.

These data are consistent either with the simultaneous interaction of the bimorphinans **1a** and **1b** with two vicinal κ opioid receptors or with binding to a κ receptor and a unique neighboring accessory site. In the first possibility, the high κ selectivity may arise as a consequence of binding to identical receptors that face each other on adjoining surfaces of associated subunits. Experiments are in progress to determine which of these possibilities confers high κ selectivity.

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(9) A solution of naltrexone hydrochloride (**2**·HCl) (1 mmol) and $RNHNH_2$·HCl (0.5 mmol) in DMF (3 mL) was heated on a steam bath for 2–6 h. The longer time periods were employed when R = Me. After conversion to the free base and workup, the crude pyrrole product was chromatographed on a silica gel column (EtOAc/NH_4OH/MeOH), reconverted to the hydrochloride salt, and rechromatographed on a gel filtration column (LH-20, MeOH). The compounds were chromatographically pure by TLC ($CHCl_3$–MeOH–NH_4OH, 18:2:1, silica gel GF) and HPLC (MeOH–TFA, 6:4, 5 μm C-8, 0.46 × 25 cm, flow rate 1 mL/min). **1a**: R_f 0.36; t_R = 6.86 min. **1b**: R_f 0.40; t_R = 6.91 min.
(10) Since both of the morphinan pharmacophores are magnetically equivalent due to C_2 symmetry, only a single set of ^{13}C and ^1H chemical shifts are observed. FAB-MS of the dihydrochloride salts afforded $(M + H)^+$: **1a**, 662; **1b**, 676.
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Table I. Opioid Antagonist Activity of Bimorphinans in the GPI and MVD

antagonist	agonist IC_{50} ratio[a] ± SEM		
	morphine[b]	ethylketazocine[b]	DADLE[c]
1a	1.6 ± 0.4	50.4 ± 9.9	2.0 ± 0.1
1b	5.4 ± 1.3	128.1 ± 16.6	4.5 ± 0.7
2 (naltrexone)	17.3	2.9	

[a] The IC_{50} value of agonist in presence of antagonist (20 nM) divided by the control IC_{50} value (no antagonist) in the same preparation (N = 6 for **1a** and **1b**). [b] Determined in the GPI preparation. [c] Determined in the MVD preparation.

for his advice and assistance. We also thank Dr. Ian Jardine for determining the FAB-MS of **1a**.

Registry No. **1a**, 105618-26-6; **1b**, 105618-27-7; **2**·HCl, 16676-29-2; NH_2NH_2, 302-01-2; NH_2NHMe, 60-34-4.

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Articles

Synthesis and Structure–Activity Relationships of a Series of Aminopyridazine Derivatives of γ-Aminobutyric Acid Acting as Selective GABA-A Antagonists

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We have recently shown that an arylaminopyridazine derivative of GABA, SR 95103 [2-(3-carboxypropyl)-3-amino-4-methyl-6-phenylpyridazinium chloride], is a selective and competitive GABA-A receptor antagonist. In order to further explore the structural requirements for GABA receptor affinity, we synthesized a series of 38 compounds by attaching various pyridazinic structures to GABA or GABA-like side chains. Most of the compounds displaced [^{3}H]GABA from rat brain membranes. All the active compounds antagonized the GABA-elicited enhancement of [^{3}H]diazepam binding, strongly suggesting that all these compounds are GABA-A receptor antagonists. None of the compounds that displaced [^{3}H]GABA from rat brain membranes interacted with other GABA recognition sites (GABA-B receptor, GABA uptake binding site, glutamate decarboxylase, GABA-transaminase). They did not interact with the Cl^- ionophore associated with the GABA-A receptor and did not interact with the benzodiazepine, strychnine, and glutamate binding sites. Thus, these compounds appear to be specific GABA-A receptor antagonists. In terms of structure–activity, it can be concluded that a GABA moiety bearing a positive charge is necessary for optimal GABA-A receptor recognition. Additional binding sites are tolerated only if they are part of a charge-delocalized amidinic or guanidinic system. If this delocalization is achieved by linking a butyric acid moiety to the N(2) nitrogen of a 3-aminopyridazine, GABA-antagonistic character is produced. The highest potency (≃250 times bicuculline) was observed when an aromatic π system, bearing electron-donating substituents, was present on the 6-position of the pyridazine ring.

It is well-known that N-alkylation of the central neurotransmitter γ-aminobutyric acid (GABA) leads to an almost complete loss of affinity for the GABA receptor site. This has been observed with monosubstituted derivatives such as *N*-methyl-GABA[1] and *N*-butyl- or *N*-phenethyl-GABA,[2] disubstituted derivatives such as *N,N*-dipropyl-GABA or 4-pyrrolidinobutyric acid (Table I), and quaternary ammonium salts such as *N,N,N*-trimethyl-GABA.[2] A similar detrimental effect has been described for muscimol.[1] However, if a secondary amino function is present in a cyclic structure as in piperidine-4-carboxylic acid, some affinity (IC_{50} = 15 μM[1]) for the GABA-A receptor is recovered. Other cyclic secondary amines derived from flexible GABA agonists such as isoguvacine, piperidine-4-sulfonic acid, and THIP (4,5,6,7-tetrahydroisoxazolo-[5,4-*c*]pyridin-3-ol) even possess high affinities.[3] For these cyclic analogues, again, N-methylation strongly weakens the potency.[3] These observations suggest that ligands for the GABA receptors are sensitive to steric hindrance at the proximity of the cationic moiety of the molecule and that the primary or secondary structure of the amino group is of minor importance. N-Acylation of GABA also led to poorly active compounds in terms of receptor binding as shown for *N*-lauroyl-GABA[4] or for *N*-*t*-BOC-GABA and

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