Opioid Agonist and Antagonist Activities of Peripherally Selective Derivatives of Naltrexamine and Oxymorphamine

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A series of β-naltrexamine and β-oxymorphamine derivatives that contain ionizable moieties coupled to the 6β-amino group were synthesized in an effort to develop antagonists and agonists that have negligible access into the central nervous system (CNS). Among the β-naltrexamine derivatives **1–7**, all displayed partial agonism on the guinea pig ileal longitudinal muscle preparation except for aspartyl derivative **6**, which was a full agonist with activity in the range of morphine. The β-oxymorphamine derivatives **8–12** were all full agonists with potencies ranging from 1.5 to 6.1 times that of morphine. Among the compounds evaluated in mice for antinociceptive or opioid antagonist activities, aspartyl derivative **6** possessed the greatest difference between peripheral (po or iv) and icv equiactive antagonist doses. Compared to naltrexone, **6** was >100 times more potent by the icv route, but 6000–10 000 times less potent when administered po or icv. The present study suggests that zwitterionic groups are highly effective in preventing penetration of ligands into the CNS. Such ligands may be useful pharmacologic tools for investigation of peripheral opioid mechanisms. Moreover, they could find clinical applications when the central actions are unwanted.

It has long been known that opioids manifest their pharmacologic effects both centrally and peripherally.[1] The primary targets for the former are the brain and the spinal cord, and these lead to a variety of pharmacologic effects, most noteworthy of which is analgesia. The major peripheral sites are located in the gastrointestinal tract. Here the effects are characterized by the ability of opioid agonists to inhibit intestinal locomotion. The antidiarrheal or constipating actions of narcotic analgesics are a manifestation of this effect. Efforts to minimize the central nervous system (CNS) effects of opiates while retaining their actions in peripheral tissue have led to the synthesis of quaternary derivatives.[2] Generally, it has been found that these quaternary compounds have considerably lower affinity at opioid receptors and substantially reduced access into the CNS relative to their tertiary amine precursors. In order to circumvent this problem of lower affinity, hydrophilic groups have been attached to a position in the molecule that is not considered detrimental to activity. This report deals with naltrexamine and oxymorphamine derivatives which contain C-6 moieties that are ionized at the pH of the gut or at physiologic pH. Since ionized groups are expected to lower lipid solubility and should reduce access into the CNS, ligands in this series were expected to exhibit greater selectivity than unionized molecules toward peripheral tissues upon peripheral administration.

Chemistry

The synthetic routes to representative target compounds (Table I) are shown in Scheme I. Compounds **1**, **2**, **4**, **8**, **10**, and **11** were obtained by reaction of the parent 6-amino opiates,[3] β-oxymorphamine (**13**) and β-naltrexamine (**14**), with the appropriate anhydride. The glycine derivative **7** was synthesized by reaction of bromoacetic acid with **14**. The fumaramic acids **3** and **9** were prepared by coupling the half-ester of fumaric acid with **13** or **14** and then subjecting the fumaramate esters to hydrolysis. The aspartyl derivatives **6** and **12** were obtained through coupling BocAsp γ-benzyl ester with the parent amines, followed by deprotection with acid to remove the Boc group and hydrogenolysis of the benzyl function. The arginyl derivative **5** was synthesized by coupling Boc-Arg(NO_2) with **13** and then deprotecting with acid and hydrogenolysis.

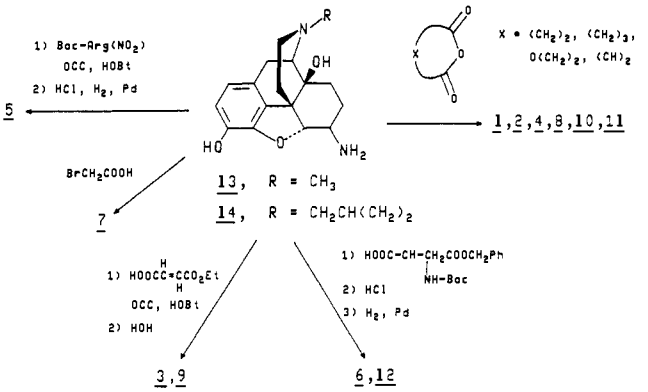
Pharmacological Results

Smooth Muscle Preparation. Opioid agonist and antagonist potencies of the compounds were assessed on the electrically stimulated guinea pig ileal longitudinal muscle[4] (GPI) preparation. The agonist potencies of naltrexamine derivatives **1–7** expressed as either IC_{50} values or maximum percent inhibition of twitch (partial agonist) are listed in Table II. The antagonism against morphine is expressed as K_e values that were derived from morphine IC_{50} ratios. All naltrexamine derivatives except **6** displayed partial agonism, with the maximum inhibition ranging from about 6% to 56%. Compound **6** possessed full agonist activity that was approximately 7 times more potent than that of morphine. All of these compounds except **6** had relatively moderate antagonist activity. The K_e values (6–28 nM) are relatively high compared to that of the parent compound naltrexone (K_e = 0.83 nM).[5] None of the compounds antagonized the action of ethylketazocine at the concentrations (20 or 200 μM) used.

The agonist potencies of the oxymorphamine derivatives **8–12** expressed as IC_{50} values and potency ratios relative to morphine are recorded in Table III. These compounds exhibited agonist potencies that were from 1.5- to 6-fold greater than that of morphine.

Antinociceptive Assay. Due to the limited quantities of compounds, only selected members of the series were evaluated in vivo. The effectiveness of the oxymorphamine

Scheme I



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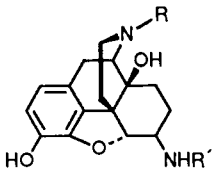
0022-2623/89/1832-2068$01.50/0

Table I. Amide Derivatives of β-Naltrexamine and β-Oxymorphamine



compd no.	R	R′	% yield	mp, °C	R_f	formula[a]
1	$CH_2CH(CH_2)_2$	$COCH_2CH_2COOH$	85	245–248	0.22[b]	$C_{24}H_{30}N_2O_6 \cdot 0.75H_2O$
2	$CH_2CH(CH_2)_2$	$CO(CH_2)_3COOH$	62	>260	0.43[c]	$C_{25}H_{32}N_2O_6 \cdot C_2H_4O_2 \cdot 0.5H_2O$
3	$CH_2CH(CH_2)_2$	*trans*-COCH=CHCOOH	86	>280	0.25[b]	$C_{24}H_{28}N_2O_6 \cdot H_2O$
4	$CH_2CH(CH_2)_2$	$COCH_2OCH_2COOH$	75	>250	0.40[d]	$C_{24}H_{30}N_2O_7 \cdot 2H_2O$
5	$CH_2CH(CH_2)_2$	$COCH(NH_2)(CH_2)_3NHC(NH)NH_2$	70	>280	0.12[e]	$C_{26}H_{39}N_6O_4 \cdot 3HCl$
6	$CH_2CH(CH_2)_2$	$COCH(NH_2)CH_2COOH$	71	>280	0.18[e]	$C_{24}H_{31}N_3O_6 \cdot 2.3HCl \cdot 2H_2O$
7	$CH_2CH(CH_2)_2$	CH_2COOH	66	>280	0.15[e]	$C_{22}H_{28}N_2O_5 \cdot 3H_2O$
8	CH_3	$COCH_2CH_2COOH$	64	218–220	0.15[f]	$C_{21}H_{26}N_2O_6 \cdot 1.5H_2O$
9	CH_3	*trans*-COCH=CHCOOH	79	>280	0.27[g]	$C_{21}H_{24}N_2O_6 \cdot 2H_2O$
10	CH_3	*cis*-COCH=CHCOOH	67	294–296	0.24[h]	$C_{21}H_{24}N_2O_6 \cdot 1.5H_2O$
11	CH_3	$COCH_2OCH_2COOH$	47	240–242	0.14[f]	$C_{21}H_{26}N_2O_7 \cdot 1.5H_2O$
12	CH_3	$COCH(NH_2)CH_2COOH$	75	>280	0.05[f]	$C_{21}H_{27}N_3O_6 \cdot 2HCl \cdot 2H_2O$

[a] Unless otherwise specified, all compounds were within 0.4% of the calculated values for C, H, N analysis for the formulas listed above. [b] EtOAc–MeOH–H_2O–NH_4OH (75:20:5:2). [c] CH_3CN–H_2O–HOAc (83:17:3). [d] EtOAc–MeOH–NH_4OH (70:30:2). [e] *n*BuOH–HOAc–H_2O (4:1:1). [f] EtOAC–MeOH–NH_4OH (50:50:5). [g] EtOAc–MeOH–NH_4OH (70:30:4). [h] EtOAc–MeOH–NH_4OH (50:50:1).

Table II. Agonist and Antagonist Potencies of Naltrexamine Derivatives in the GPI Preparation

compd	agonism:[a] % inhibn[b] or IC_{50}, nM	antagonism:[a] K_e,[d] nM
1	56 ± 3 (3)	24.8 ± 6.9
2	41 ± 9 (4)	28.0 ± 3.2
3	6 ± 5 (3)	8.4 ± 2.2
4	38 ± 7 (3)	6.2 ± 0.9
5	28 ± 16 (4)	9.5 ± 3.3
6	7.4 ± 2.0 (3)[c]	*e*
7	37 ± 4 (3)	24.4 ± 10.9

[a] Values are means ± SE. [b] The maximum percent of inhibition of the electrically stimulated twitch was determined at a concentration of 1 μM. Parentheses contain the number of experiments. [c] IC_{50} value. [d] Antagonism to morphine, K_e = [antagonist]/(IC_{50} ratio − 1), where the IC_{50} ratio is equal to the IC_{50} of morphine in the presence of antagonist divided by its control IC_{50} in the same preparation. [e] Agonism was too strong to test for antagonism.

Table III. Agonist Potency of Oxymorphamine Derivatives on the GPI Preparation[a]

compd	$IC_{50} \times 10^8$ M	potency ratio[b]
8	14.4 ± 9.4 (5)	1.6 ± 0.9
9	13.0 ± 6.0 (3)	1.5 ± 0.3
10	3.9 ± 2.2 (3)	2.6 ± 1.2
11	2.7 ± 0.6 (3)	3.1 ± 0.6
12	3.1 ± 1.0 (3)	6.1 ± 2.8

[a] Values are means ± SE. Parentheses contain the number of experiments. [b] Morphine = 1.

derivatives 8 and 10–12 was assessed by injecting these compounds into male Swiss–Webster mice and monitoring the antinociceptive activity using the tail-flick procedure[6] (Table IV). All compounds possessed relatively high antinociceptive activity when administered by the intracerebroventricular route (icv). The compounds also were active when administered iv, but the ED_{50} doses were much higher than those after icv administration. When compared on a body-weight basis, the intravenous (iv) ED_{50} doses were about 1000 times higher than the icv ED_{50} values. Unexpectedly, compounds 8 and 10 also were active when given orally (po). There was insufficient amount of drug to test 11 and 12 orally. The oral ED_{50} doses were

Table IV. Antinociceptive Potencies of Oxymorphamine Derivatives in Mice[a]

compd	route of adminstrn	peak effect, min	ED_{50} (95% CI)
8	icv	40	0.27 (0.13–0.53) nmol/mouse
	iv	40	9.8 (9.6–10.0) μmol/kg
	po	60	30.3 (9.3–158.5) μmol/kg
10	icv	20	0.17 (0.05–0.33) nmol/mouse
	iv	20	11.0 (3.0–31.8) μmol/kg
	po	60	~20 μmol/kg[b]
11	icv	40	0.25 (0.09–0.50) nmol/mouse
	iv	40	<20 μmol/kg[c]
	po	60	>25 μmol/kg[c]
12	icv	20	0.44 (0.39–0.50) nmol/mouse
	iv	40	<20 μmol/kg[c]

[a] The tail-flick assay was used. [b] Estimated on the basis of two dose levels. [c] Insufficient amount of drug for full test. Approximate range of dose is based on one dose level.

3–4 times those of iv administration.

The aspartyl derivative of naltrexamine 6 was of interest for further study because of its unusually high agonist potency in the GPI and its zwitterionic property. This compound did not possess any agonist activity, even at very high doses (150 nmol, icv), when tested by the tail-flick assay. However, in the writhing assay, 6 exhibited very high antinociceptive potency when administered icv (Table V). This ligand also was active when given orally; however, the oral ED_{50} dose was nearly 230 000 times that of the icv ED_{50} dose on a body-weight basis.

To test for the antagonist activity of 6 against the antinociceptive effect of morphine in mice, the tail-flick method was used because 6 showed no agonist activity in this test. Morphine was administered subcutaneously (sc), 6 was given by different routes (icv, iv, or po), and testing was synchronized so that it was done at the peak time of activity for both the agonist and the antagonist. The peak time of activity of 6 after administration by various routes was determined in separate experiments. Antagonist activity of 6 was observed when it was administered by all three routes of administration (Table V).

The doses (icv, iv, and po) of 6 and naltrexone required to effect an equivalent antagonism of morphine activity were calculated and are listed in Table VI. The po dose of 6 was 28 times higher than the iv dose, and the iv dose was >13 500 times higher than the icv dose on a body-weight basis. This suggests that approximately 4% of the

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Table V. Agonist and Antagonist Potencies of 6 in Mice

A. Agonism (Acetic Acid Writhing Assay)

route of adminstrn	peak effect, min	ED_{50} (95% CI)
icv	10	0.024 (0.021–0.028) nmol/mouse
po	60	0.22 (0.20–0.24) mmol/kg

B. Antagonism (Tail-Flick Assay)

route of adminstrn	dose	peak effect, min	ED_{50} of morphine,[a] μmol/kg	dose ratio
no treatment			13.8 (10.3–18.7) (control)	
icv	0.01 nmol	60	58.0 (43.5–78.0)	4.2 (2.7–6.3)
iv	18.3 μmol/kg	90	167.9 (133.4–220.6)	12.2 (8.3–16.7)
po	91.7 μmol/kg	120	41.4 (31.6–51.7)	3.0 (2.0–4.2)

[a] Tested 30 min after sc injection.

Table VI. Comparison of Doses of 6 and Naltrexone Given by Various Routes of Administration

route of adminstrn	dose required to produce equivalent antagonism[a]	
	6	naltrexone
icv	0.003 nmol/mouse[b]	0.35 nmol/mouse[b]
iv	1.63 μmol/kg	0.02 μmol/kg
po	45.85 μmol/kg	0.79 μmol/kg

[a] Dose required to double the ED_{50} of morphine [dose/DR − 1]. [b] These doses calculate to 0.12 nmol/kg body weight for 6 and 14 nmol/kg for naltrexone.

oral dose of 6 is absorbed and <0.01% of the iv dose enters the brain.

Compared to naltrexone, 6 was more than 100-fold more potent when administered icv. On the other hand, naltrexone was at least 60 times more potent than 6 when administered by the po or iv routes.

Discussion

All of the compounds (Table I) in the present series possess groups that should be highly ionized at physiologic pH or at the pH of the gut. We envisaged that such compounds would not have easy access to the CNS and hence be useful as peripherally acting opioid agonists or antagonists.

Among the naltrexamine derivatives 1–7, only aspartyl analogue 6 behaved as a full agonist in the GPI preparation (Table II). It appears that modification with different amide functions affords ligands with reduced antagonist potency and partial or full agonist activity. In this connection, the most potent antagonist in this series, 3, was about $^1/_{10}$ as active as naltrexone. This represents less of a potency loss than for quaternary naloxone derivatives, where the antagonist potency and binding affinity has been reported to be only 2–4% that of naloxone.[8-12]

The strong agonism (7-fold that of morphine) of 6 in the GPI (Table II) was unexpected, but not without precedent for *N*-cyclopropylmethyl-substituted opiate structures. There are a number of examples where substitution in the 6-position affords agonists when tested in the GPI preparation.[13-15] In such cases, evidence has been presented which suggests that the agonist component is mediated via interaction of the ligand with κ receptors; the antagonist component, which arises from interaction with μ receptors, is completely masked by this agonist effect.

The oxymorphamine members 8–12 (Table III) of this series all were more potent agonists than morphine, with aspartyl derivative 12 having the greatest potency (6 times that of morphine). Since the agonist potencies of these opiates (e.g., 10–12) are in the range of oxymorphone, it appears that C-6 substituents with ionizable groups do not have a significant adverse effect on agonist activity at the receptor level.

The oxymorphamine derivatives were potent antinociceptive agents when administered icv to mice (Table IV), with ED_{50} values in the subnanomolar range. These potencies did not differ significantly from one another. As expected, the iv ED_{50} were thousands of fold higher. However, where sufficient compound was available (8, 10), the po ED_{50} values differed from the iv ED_{50} doses by only small factors.

Due to the limited quantity of compounds in the naltrexamine series, only the aspartyl derivative 6 was evaluated in vivo (Table V). Significantly, this compound was a potent agonist in the writhing assay and a potent antagonist in the tail-flick assay. These results are consistent with reports that the writhing assay is sensitive to the antinociceptive effect of κ agonists, while the tail-flick assay is sensitive to μ agonists and insensitive to κ agonists.[16-19] Thus, the in vivo agonist activity of 6 is most likely mediated via κ receptors, whereas its in vivo antagonist activity is due to a μ opioid receptor antagonist component.

Predictably, the po doses of 6 to produce equivalent antagonism (Table VI) were many orders of magnitude larger than the icv equiactive doses. The fact that 6 was 28 times more effective, iv relative to po, is in contrast to other compounds (e.g., 8 and 10) where the ratios amounted to a factor of only 2 or 3. This difference reflects the zwitterionic nature of the aspartyl residue in 6, as it is considerably more polar than the maleamate or succi-

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namate groups, and this undoubtedly is a factor in the very high icv/po activity ratio observed for **6**.

That the zwitterionic nature of **6** is indeed important in limiting penetration into the CNS was demonstrated by comparing its po, iv, and icv antagonist potencies with those of naltrexone (Table VI). Thus, naltrexone was 6000–10 000 times more potent than **6** when administered peripherally, but by the icv route **6** possessed >100 times greater potency than naltrexone.

Conclusion

The present study suggests that attachment of polar groups, particularly zwitterionic moieties, at the C-6 position of the morphinan structure is effective in excluding such ligands from the CNS, thereby affording peripheral selectivity. Such modification does not appear to compromise the receptor activity of these compounds to a great degree.

Ligands in this series may be useful as pharmacologic tools in the investigation of opioid mechanisms at peripheral sites. Also, such compounds could find clinical applications where the central actions of opioids or opioid antagonists are unwanted.

Experimental Section

Melting points were determined with a Thomas-Hoover capillary melting point apparatus and are uncorrected. Elemental analyses were performed by M-H-W Laboratories, Phoenix, AZ. All analytical results were within ±0.4% of the theoretical values. IR spectra were recorded on a Perkin-Elmer 281 spectrophotometer. NMR spectra were recorded on either a JNM-FX 90Q FT NMR spectrometer or a Nicolet 300-MHz NMR spectrometer with tetramethylsilane as internal standard. Mass spectra were obtained on an AEI M5-30 (EI, 20 eV) or a Finnigan 4000 (CI, NH_3, positive or negative). All R_f values were obtained on Analtech silica gel TLC plates.

Compounds 1, 2, 4, 8, 10, 11. The appropriate acid anhydride (succinic, maleic, glutaric, or 3-oxyglutaric) (0.33 mmol) was dropped over a 1-h period into a dimethylformamide (2.5 mL) solution containing 0.33 mol of β-naltrexamine (**14**) or β-oxymorphamine (**13**). After stirring for an additional 3 h at room temperature, the mixture was poured into ether (50 mL) and the precipitate was collected by filtration. Crystallization from acetone or aqueous acetone afforded the pure acids.

Fumaramic Acids 3 and 9. To a mixture of the dihydrochloride of **13** or **14** (0.62 mmol), triethylamine (0.35 g, 2.48 mmol), and dimethylformamide (2 mL) that was stirred at 25 °C for 15 min were added fumaric acid monoethyl ester (0.089 g, 0.68 mmol) and 1-hydroxybenzotriazole (0.189 g, 1.24 mmol). Dicyclohexylcarbodiimide (0.192 g, 0.93 mmol) was then added to the cooled mixture (0 °C), which was stirred at 0 °C for 1 h and then at 25 °C for 10 h. The reaction mixture was poured into water (50 mL) containing sodium carbonate, and the mixture was extracted with ethyl acetate (5 × 25 mL). After removal of the solvent in vacuo, the product was chromatographed on silica gel (EtOAc–MeOH–Me_3N, 90:10:0.5) to afford the ethyl ester intermediates that were hydrolyzed in ethanolic NaOH (0.5 N, 5 mL) at 25 °C for 10 h. The mixture was adjusted to pH 8 with 1 N HCl and the solvent was removed in vacuo. The product (**3** or **9**) was purified by chromatography on silica gel (EtOAc–MeOH–NH_4OH, 70:30:4).

Arginyl-β-naltrexamine (5). β-Naltrexamine dihydrochloride (0.415 g, 1 mmol) was suspended in DMF (3 mL), and TEA (0.3 mL) was added. After cooling to 0 °C, Boc-Arg(NO_2) (0.319 g, 1 mmol), HOBt (0.405 g, 3 mmol), and DCC (0.210 g, 1 mmol) were added. The reaction was stirred at 0 °C for 1 h and at 25 °C for 12 h. The mixture was filtered and washed with DMF (0.5 mL). To the filtrate was added 10% $NaHCO_3$ (50 mL), and the mixture was extracted with ethyl acetate (3 × 50 mL). The ethyl acetate was dried ($MgSO_4$) and the solvent was evaporated in vacuo. The residue was triturated with ethyl ether, and the solid formed was filtered and washed with ether. The nitroarginyl intermediate (0.610 g, 95% yield), mp 153–156 °C, was dissolved in 4 N HCl in ethyl acetate (10 mL), and after 20 min, 10 mL of ethyl acetate was added. This solid was filtered and washed with ethyl acetate: yield, 0.510 g (73%); mp 258 °C dec; R_f = 0.18 (nBuOH–AcOH–H_2O, 4:1:1). Arg(NO_2)-β-naltrexamine dihydrochloride (400 mg, 0.57 mmol) was dissolved in methanol (15 mL), and 10% Pd/C (50 mg) and concentrated HCl (0.3 mL) were added. After hydrogenation for 24 h, the catalyst was removed by filtration and the solvent was evaporated in vacuo. The residual solid was precipitated by addition of EtOAc to afford 370 mg (96%) of **5**, mp >280 °C, R_f = 0.12 (nBuOH–HOAc–H_2O).

Aspartic Acid Derivatives 6 and 12. A mixture of the dihydrochloride of **13** or **14** (1.0 mmol), triethylamine (0.3 mL), and dimethylformamide (5 mL) was stirred at 25 °C for 15 min. After cooling in ice bath to 0 °C, Boc-aspartic acid monobenzyl ester (0.323 g, 1.0 mmol) and 1-hydroxybenzotriazole (0.405 g, 3.0 mmol) were added. Dicyclohexylcarbodiimide (0.206 g, 1 mmol) then was added and stirring was continued at 0 °C for 1 h and at 25 °C for 10 h, and the mixture was filtered. The filtrate was poured into 1 N sodium carbonate (40 mL) and the product was extracted with EtOAc (4 × 25 mL) and washed 3× with 1 N Na_2CO_3. After removal of the solvent in vacuo, the residue was treated with 2 N HCl (5 mL) in HOAc (5 mL) containing 1 drop of anisole. After 15 min at 23 °C, MeOH (10 mL) and 10% Pd/C (50 mg) were added, and the mixture was hydrogenated with stirring for 4 h. The mixture was filtered and the solvent was removed in vacuo to afford a solid, which was crystallized from EtOH–EtOAc.

β-Naltrexamineacetic acid (7). β-Naltrexamine dihydrochloride (0.415 g, 1 mmol) was suspended in acetonitrile (7 mL) and diisopropylethylamine (0.61 g, 3.5 mmol) was added. After 10 min, bromoacetic acid (0.153 g, 1.1 mmol) was added to the reaction mixture and it was allowed to stand at 25 °C for 10 h. After removal of solvent, the solid residue was crystallized from hot 2-propanol containing 1% MeOH to afford 0.265 g (66%) of **7**, mp >280 °C.

Acknowledgment. This research was supported by the National Institute on Drug Abuse. We thank Victoria Darrow Elliot and Mary Schwartz for the capable technical assistance.