Chapter 5. *Narcotic Analgetics, Endorphins and the Opiate Receptor*

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Reviews on the endorphins[1-4] and other aspects of opiate research[5-7] have appeared. Research on the opiates has centered on 1) the elucidation of the physiological locations and the functions of endorphins; 2) the discovery of peptide or classical narcotic structural analogs which are clinically effective for the relief of pain but lack addiction liability;[8] 3) the determination of the nature of the opiate-receptor(s). The major advancements in each of these areas are reviewed in this chapter.

Endogenous Opiates

Biosynthesis and Catabolism - Evidence continues to mount that endorphins in the pituitary gland are derived from a larger precursor by the pathway[9-11]: 31K peptidal precursor → β-Lipotropin → β-Endorphin → γ-Endorphin → α-Endorphin. ACTH is also derived from the 31K peptide. Met-enkephalin can be derived from the degradation of larger endorphins; however, the importance of this pathway remains uncertain.[12] The origin of leu-enkephalin remains unknown. The activities of the enkephalins are terminated by the rapid cleavage of the Tyr-Gly peptide bond.[13-15] This cleavage limits the duration of action of these agents and makes quantitative measurements of their activity difficult in all *in vivo*, and some *in vitro*, tests.

Distribution - Immunohistochemical,[16-20] radioimmunoassay,[21-24] stereospecific receptor binding,[25-26] and electrically stimulated mouse vas deferens[27] assays were used to map endorphin distribution in several animal species. These studies agree that the larger peptidal endorphins have higher concentration in the pituitary than in other regions of the brain or other tissues. Conversely, the enkephalins predominate in nonpituitary tissues. Within the rat pituitary the endorphins are located in cells of the pars intermedia and pars distalis but are excluded from the neurophypophysis. In rats the enkephalins are distributed in regions of the spinal cord, regions of the brain including the periaqueductal grey matter, thalamus, hypothalamus, and basal ganglia, and in the gut. Studies using either decapitation or microwaves to kill rats have produced equivalent results;[26] however, these results apparently depend on the procedures used to kill the rats.[24] Radioimmunoassays using met-enkephalin specific[18] or met- and leu-enkephalin nonspecific antibodies[21] show equivalent enkephalin distribution patterns indicating that there is little anatomical separation between the two peptides. The distribution of the enkephalins parallels the distribution of opiate receptors in many, but not all, brain regions.

Physiological Actions and Functions - The exact physiological function of endogenous opiates remains unknown.[28] Evidence continues to mount that exogenously administered endorphins and enkephalins produce morphine-like actions in animals.[29] Studies show that met-enkephalin inhibits the morphine abstinence syndrome in mice.[30] β-Endorphin administration to animals

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causes analgesia and development of tolerance to its analgetic effects.[31-35] Analgesia is produced by injection of enkephalins into areas of the spinal cord.[34-35] The self-administration of the enkephalins by mice suggests that, like morphine, the enkephalins cause euphoria and drive-reduction reward.[36] Rats self-administer leu-enkephalin to a greater extent than met-enkephalin, indicating that leu-enkephalin may play a predominant role in euphoria and behavioral aspects of opiate activity.[36] Leu-enkephalin produced a morphine-like analgetic effect when injected intracerebroventricularly (i.c.v.) into rats (45°C hot-plate); however, when tested in a similar manner, met-enkephalin caused an increased sensitivity to pain and induced reponses resembling those seen in narcotic withdrawal. Injection (i.c.v.) of β-endorphin into cats caused behavioral responses at 12.5 μg and both behavioral and antinociceptive responses at 25.0 and 50.0 μg doses; however, no effect from met-enkephalin was observed.[38] Analgesia, antagonized by naloxone, was produced by met-enkephalin injected into the periaqueductal grey matter of rats.[39] Amnesia produced in rats by enkephalins is not reversed by naloxone.[40] β-Endorphin also inhibits fixed ratio operant behavior in rats.[41] Large doses (1-2 mg) of met-enkephalin injected (i.c.v.) into cats caused emetic and hyperthermic effects similar to those caused by morphine.[42] Hypermotility in rats, which is blocked by naloxone but not haloperidol, is produced by injection of morphine or D-ala-met-enkephalin amide into the nucleus accumbens of rats.[43]

The putative role of enkephalins as neurotransmitters is enhanced by studies which show that electrical stimulation (10 Hz) of guinea pig ileum strips causes release of enkephalins.[44,45] This preparation may provide a valuable model for the study of the synthesis, storage and release of endorphins.[44] The inhibitory effects of met- and leu-enkephalins have been shown on acetylcholine release in myenteric plexus neurons.[46] Inhibition of acetylcholine release and turnover by the enkephalins has been shown in brain tissues.[47-49] The enkephalins have similar inhibitory effects on some dopamine[49,50] and substance P mediated neurons.[51] Microiontophoretic application of endogenous opiates into rat brains showed an inhibitory response on all responsive cells[52,53] except those in the hypothalamus where these compounds caused an excitatory response.[54]

The endorphins cause an opiate-like inhibition of c-AMP formation in neuroblastoma X glioma hybrid cells.[55-57] The effects of endorphins on the release or physiological blood levels of prolactin, luteinizing hormone, follicle stimulating hormone, thyroid stimulating hormone, growth hormone and arginine vasopressin have been studied.[58-62]

The hypothesis that endogenous opiates function in modulating severe stressful or painful stimuli is supported by the elevated endorphin levels found in dehydrated[63] and foot-shock stressed[64] rats. This effect has not been shown in man.[65] Treatment of depressed patients with naloxone failed to give noticeable improvement although the naloxone treatment did cause a decrease in CSF endorphin levels.[66] Naloxone also failed to produce significant effects when tested in a double-blind experiment on schizophrenic patients.[67] Naltrexone, in high doses, does not have beneficial effects on schizophrenic patients.[68] Naloxone causes a dose related antianxiety effect in man.[65] Injection (i.v.) of 1.5 mg of β-endorphin into three

schizophrenic patients exacerbated their clinical condition; however, a similar dose of β-endorphin to two depressed patients resulted in marked improvement of their condition.[69] A subsequent treatment of these same patients with β-endorphin obtained from a different synthetic preparation failed to produce the results of the first studies.[69]

Conformation of Enkephalins - Studies continue to show a great deal of conformation mobility for enkephalins and there is disagreement as to the most probable conformation in solution.[70-74] Some of the discrepancies in NMR conformational studies can be explained from the fact that spectral changes occur on dilution with dimeric structures existing at high concentrations,[70] and that the enkephalins can exist in zwitterionic and cationic forms which differ in spectral features.[71] Theoretical studies indicate a number of possible low energy conformations.[75,76] Conformations with a type βII-bend at or a type βI-bend at position 3 and 4 have been proposed. Either of these enkephalin conformations have some structural parameters in common with synthetic opiates.[70,71] A study has been made with a series of enkephalin analogs in which mouse vas deferens activity and receptor binding in brain homogenates were correlated with allowable conformations of the peptide chain. By this procedure a conformational map showing enkephalin conformations allowable for activity was constructed.[77]

Enkephalin Analogs - Selected enkephalin analogs which have been prepared in an attempt to discover analgetic agents with improved pharmacological profiles are reported in Table I. Compound 9 (FK 33-824) is 1000X more potent than morphine (mouse hot-plate, i.c.v.).[85] This compound retains one-fifth the activity of morphine when given orally. A D-amino acid in place of Gly^2 facilitates oral or i.v. activity by decreasing metabolic inactivation of the peptides. Studies have shown that 1 and 9 retain the addicting properties of morphine.[79,85] No peptide with analgetic activity has been reported to be nonaddicting. The enkephalin analogs do have decreased respiratory effects compared to morphine; however, they produce a catatonic state which is unlike morphine's action.[84,85] The danger of depending on *in vitro* tests to measure analgetic potency is demonstrated by the high *in vitro* activities seen for hexapeptides 12[84] 13[86] which were poorly active or inactive *in vivo*.

Reports on the agonist-antagonist activity of several N-allyltyrosyl analogs of enkephalins have appeared. N-Allyl-[D-ala]^2- met-enkephalin[87] and N-allyl-met-enkephalin[87,88] were found not to have appreciable antagonist properties. N-Allyl-leu-enkephalin does have antagonist activity on the guinea pig ileum.[88]

Miscellaneous Endogenous Opiates - Two compounds having opiate-like activity have been detected in the blood of several animal species. These two compounds, called slow moving material (SMM) and fast moving material (FMM) on the basis of their tlc behavior, are not degraded by pronase and show different activities on guinea pig ileum than β-endorphin or met-enkephalin.[89] A nonpeptide morphine like substance (MLS) has been isolated from beef brains and human urine.[90] MLS binds with a specific anti-

Table I. Selected Enkephalin Analogs.

No.	Identification Number	Structural Variations at a.a. Position					Ref.
		1	2	3	4	5	
1	BW180c	H-Tyr	D-Ala	Gly	Phe	D-Leu-OH	78,79
2	ICI120,518	H-Tyr	D-Ala	Gly	Phe	Pro-NHEt	80
3	ICI121,444	H-Tyr	D-Ala	Gly	Phe-NH-		80
4		H-Tyr	D-Met	Gly	Phe	Pro-NH_2	81
5		H-Tyr	D-Met	Gly	Phe	Pro-NHEt	81,82
6		H-Tyr	D-Ala	Gly	Phe	Met-OH	83
7		H-Tyr	D-Nle	Gly	Phe	Pro-NHEt	82
8		H-Tyr	Gly	Gly	Phe	Leu-NH-CH_2-CH_2-$NHCH_3$	84
9	FK33-824	HTyr	D-Ala	Gly	N-Me-Phe	Met(O)-ol	85
10		HTyr	D-Ala	Gly	Phe	Met-ol	85
11		HTyr	D-Ala	Gly	Phe	Met-(O)-ol	85
12		H-Lys-Tyr	D-Ser	Gly	Phe	Met-OMe	84
13		H-Arg-Tyr	Gly	Gly	Phe	Met-OH	86

body to morphine which does not cross react with peptide opiates. MLC binds to opiate receptors in neuroblastma X glioma hybrid cells in a similar fashion to, but 20-40X greater than, naloxone.

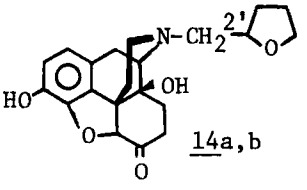
Nonpeptide Opiate Agonists and Antagonists

Oripavines - Detailed animal pharmacology of buprenorphine has been reported.[91,92] Buprenorphine is more potent and longer acting as an analgetic, shows less addiction liability, and causes less respiratory depression at high doses, when compared to morphine sulfate.

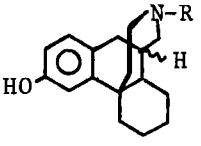
Morphines and Morphinans - Double-blind[93,94] and placebo-controlled[95] studies with butorphanol show it to be an effective analgetic agent in man. An evaluation of heroin in terminal cancer patients will be made.[96] Formyl and propionyl homologs of 6-acetyl- and 3,6-diacetylmorphine were shown to have 4X longer duration than morphine in monkeys.[97] The (+)-isomer of morphine was synthesized and shown not to be an analgetic, but to retain some of the pharmacological effects of opiates.[98] Multiple receptors were proposed on the basis of the activity of (+)-morphine.

The N-(2'R)-tetrahydrofurfuryl derivative 14a (Mr 2096 CL) was reported to be a mixed agonist-antagonist with 25X the potency of morphine in the mouse writhing test and to partially suppress morphine abstinence in monkeys.[99,100] The epimeric 2'S-analog 14b is a pure antagonist with 0.2 the activity of nalorphine.

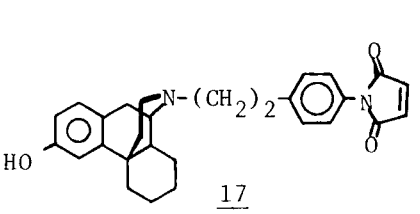
Homo- and homoisomorphinan derivatives 15a,b, and 16a,b were reported.[101] Both 15a and 15b are equipotent with morphine in the hot-plate test; however, 15b supports physical dependence while 15a neither sup-



14a,b



	cis B/C	tran B/C	R
	15a	15b	Me
	16a	16b	CH_2-



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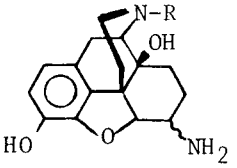


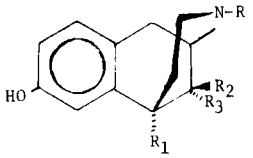
18a,b R = allyl

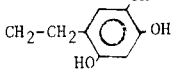
19a,b R = CH_2-c-C_3H_5

presses nor precipitates withdrawal in monkeys. The cyclopropylmethy derivatives (16a,b) have 0.12 and 0.05 the analgetic activity of morphine, lack antagonist activity and do not substitute for morphine in addicted monkeys. Compound 17, a representative example of a series of N-aralkylmorphinans prepared as potential opiate receptor-site-directed alkylating agents, was 4X as potent as morphine sulfate in the hot-plate test and caused some inhibition of morphine activity in this same test. Receptor binding studies failed to show irreversible binding of 17.[102] Epimeric 6-amino derivatives 18a,b and 19a,b, were found to be less potent, but longer acting antagonists than their keto precursors, naloxone and naltrexone.[103]

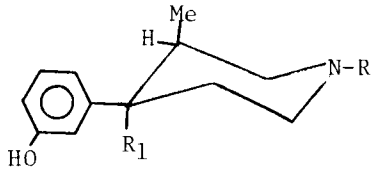
Benzomorphans - An excellent review on synthetic and chemical aspects of the benzomorphans was published.[104] A controlled treatment study confirmed that naltrexone produced fewer side effects than cyclazocine in man.[105] A "twin crossover relative potency analgesic assay" in man comparing morphine and 8-methoxycyclazocine (Win 20,836) revealed that doses of 8-methoxycyclazocine equianalgetic with a morphine standard caused unacceptable levels of psychotomimetic side effects.[106]

Compounds 20 and 21 gave respectively 0.20 and 1.0 the analgesia of morphine in the hot-plate test.[107] Antagonist activity greater than that of nalorphine was seen for 21, but 20 is not an antagonist in the tail-flick screen. Neither 20 nor 21 suppressed abstinence signs in morphine dependent monkeys. Benzomorphan analogs 22 and 23 incorporate the 9β-OH in the position equivalent to the 14-position of the morphinan ring nucleus.[108] Compound (-)-22 is equipotent as an agonist (mouse writhing) and 2X more potent than butorphanol as an antagonist (straub tail test). Compound 23 is virtually devoid of agonist activity but slightly more active than naloxone as an antagonist.



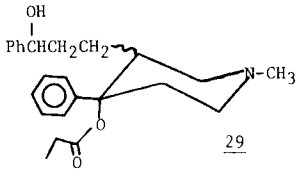
	R	R_1	R_2	R_3
20	n-C_6H_{13}	Me	Et	H
21	CH_2-c-C_4H_7	Me	Et	H
22	CH_2-c-C_3H_5	allyl	OH	H
23	CH_2-c-C_4H_7	allyl	OH	H
24	Me	Me	$(CH_2)_2$-C(OH)(CH_3)-$(CH_2)_3$-H	H
25	CH_2-c-C_3H_5	Me	$(CH_2)_2$-C(OH)$(CH_3)_2$	Me
26	CH_2-c-C_3H_5	Me	$(CH_2)_2$-C(OH)(CH_3)-C$(CH_3)_3$	Me
27		Me	H	Me

A series of eighteen benzomorphans with 9-propanol substituents, as in oripavine structures, included compounds 24,25 and 26.[109] These compounds had agonist ED_{50}'s of 2.6,4.5 and >25 mg/kg (acetylcholine writhing) and antagonist AD_{50}'s of >80, 0.006, and 0.022 mg/kg (phenazocine antagonism) respectively, compared to values of 2.8 (ED_{50}) and 0.1 (AD_{50}) for nalorphine. A series of N-substituted 9α-n-propyl-6,7-benzomorphans was prepared and the $N-CH_3$ to $N-C_6H_{13}$ derivatives found to have potent (unquantified) and long lasting (to 10 hr) antagonist effects in single dose suppression studies in monkeys.[110] The N-(2,4,5-trihydroxyphenylethyl)normetazocine derivative 27 was prepared in an attempt to deliver a 6-hydroxydopamine-like alkylating moiety to the analgetic receptor; however, this compound has only weak affinity for the opiate receptor (neuroblastoma X glioma cells).[111] The C-ring-N-positional analog of the benzomorphans possesses activity equivalent to codeine (mouse tail pressure).[112] The B,C-methano-bridged analog gave nalorphine level antagonism (rat tail-flick) but only weak agonist effects.[113]



	R	R_1
28a	Me	Me
28b	phenethyl	Me
28c	Me	propiophenone
28d	Me	propionoxy

4-Phenylpiperidines - The most exciting report in this area was the potent and pure antagonist activities seen for the 4-(3-hydroxyphenyl)-3-methylpiperidine derivatives of structure 28.[114] Thus 28a, 28b and 28c had AD_{50} values of 0.24, 0.11 and 0.056 mg/kg, s.c. ("rat tail heat" against morphine), respectively, compared to a value of 0.022 mg/kg for naloxone. The (+)-isomer of 28a (AD_{50}=0.029) is more active than the (-)-isomer (AD_{50}=0.22). The cis-3,4-Me compounds are 50-100X less active. The 3-methyl group is believed to confer antagonist properties to this compound since the β-prodine analog 28d is a pure antagonist 2-3X more potent than pentazocine. N-Allyl derivatives of 28 are less potent as antagonists than their N-methyl counterparts.



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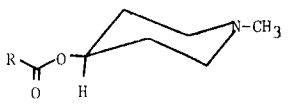
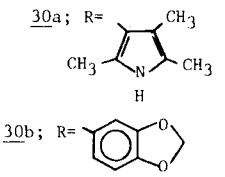
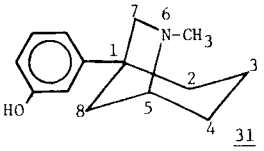




The correlation observed between receptor binding and hot-plate analgesia of α- and β-prodine analogs substituted with Me, Et, allyl and hexyl at the 3-position led to the conclusion that activity in this series is determined by relative receptor affinity rather than distribution and/or metabolism of the compounds.[115] The ester 29, of 3-(3-hydroxy-3-phenylpropyl)piperidine was inactive in the tail-flick test but was a weak agonist in the writhing test (80.5 and 32 mg/kg respectively).[116] 1-Methyl-4-piperidinol esters with bulky aromatic substituents gave codeine

level analgetic activity (4.9, 7.3 mg/kg for 30a and 30b, respectively) in the mouse hot-plate test. These compounds showed only weak binding (300-30,000X less than morphine) to opiate receptors in mouse brain homogenates and 30b had no dependence liability in monkeys.[117]



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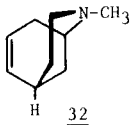

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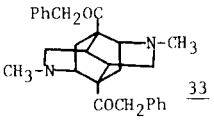

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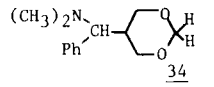

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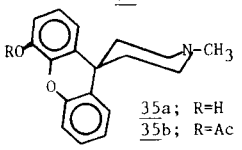
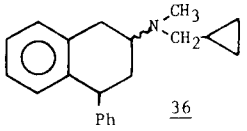


35a; R=H
35b; R=Ac



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Miscellaneous - Extensive SAR on the 6-azabicyclo[3.2.1]octanes (31) were published.[118] Methyl substitution at C-7 enhances agonist activity (7-Me-N-Me, ED_{50}=2.9; hot-plate test) while a methyl at C-8 gives compounds which are inactive as agonists but retain antagonist activity (8-Me-N-Me, AD_{50}=0.18 vs. 0.16 for nalorphine; morphine respiratory depression, rabbits). 7,8-Dimethyl substitution results in inactive compounds. SAR of N-substituted analogs somewhat parallel that observed for other analgetic series with exception of the N-phenethyl substituent which is inactive in the nonmethylated ring system but in combination with a 7-Me substituent produced the most potent agonist of the series (ED_{50}=0.3 mg/kg vs. 1.2 mg/kg for morphine; hot-plate test). None of the compounds displayed appreciable physical dependence capacity. The N-Me-7,8-unsubstituted and the N-Me-7-exo-methyl compounds were resolved and only the (+)-isomers found to be active as agonists; however, the (-)-isomers maintained antagonist activity. Members of other bicycloalkane series such as the 3-hydroxyphenyl derivatives of 2-azabicyclo[2.2.2]octane,[119] 2-azabicyclo[3.2.1]octane[120] and 3-azabicyclo[3.3.1]nonane[121] were inactive as agonists but produced pentazocine level antagonism in the rabbit respiratory depression assay.

The B,C-ring analog (32) of morphine was synthesized but failed to show analgetic activity.[122] The (-)-isomer of the novel 5,11-diazaditwistane derivative 33 had analgetic activity 2X greater than morphine (rat hind paw pressure) while the (+)-isomer was inactive.[123] The (+)-isomer of the 1,3-dioxane 34 gave analgetic activity comparable to codeine (ED_{50}'s 6.2 vs. 6.7 mg/kg, AcOH writhing)[124] which was blocked by naloxone. Replacement of the phenyl with 3-pyridyl or a 2-Me substituent on the dioxane ring gave a 2-3 fold increase in agonist activity. The spiroperidine analogs 35a (ICI 86,458) and 35b (ICI 91,356) are reported to have 0.5 and 1.0 the potency of morphine in the AcOH writhing assay.[125] Both the cis- and trans-aminotetralin diastereomers of 36 were reported to have codeine level agonist activity (mouse hot-plate) and, at 3 mg/kg, to give a 100% inhibition of an ED_{80} dose of morphine (mouse tail flick).[126]

Opiate Receptors

The differential competitive displacement by narcotic agents of various ^{3}H-labeled peptide and nonpeptide opiates from receptors (stereospecific binding sites) in brain tissue has led a number of investigators to conclude that there are multiple receptors associated with opiate activity.[127-131] The contention of multiple receptors is augmented by the differential *in vitro* and *in vivo* pharmacological responses seen with various opiates.[131-135] An example of this is the equipotent activities seen for morphine and met-enkephalin on the guinea pig ileum compared to 30X greater activity of met-enkephalin on the mouse vas deferens.[131]

A quantitative relationship between opiate receptor binding and activity *in vivo* could be made for ten structurally diverse opiates when lipophilicity was also taken into account.[136] Cases have been reported in which binding ratios in the presence and absence of Na^{+} failed to predict the narcotic antagonist activity which undoubtedly existed in the compounds. Also, some pure agonists have been found to have low sodium binding ratios.[137] Two proposals on the nature of the opiate receptor appeared. One of these is similar to the Beckett model but proposes an extended aromatic (lipophilic) binding region.[138] The other pictures the receptor site as a cup shaped area formed by four pentapeptide segments in antiparallel β-pleated sheets.[139] As with all previous opiate receptor models, both of these proposals are based on SAR correlations of some, but not all agents having opiate activity and neither are supported by experimental evidence.

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