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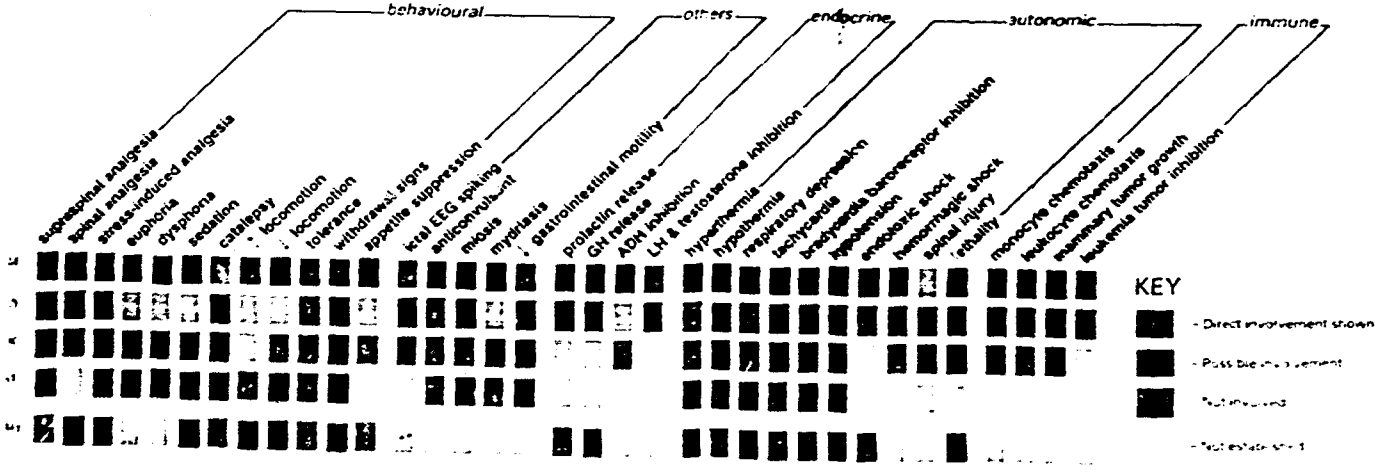
# OPIATE RECEPTOR SUBTYPES



| Receptor subtype | Endogenous agonists | Endogenous agonist structure | Endogenous agonist precursor | Prototype agonist | Selective agonists | Selective antagonists | In-vitro assay system |
|---|---|---|---|---|---|---|---|
| μ | β-endorphin | Tyr-Gly-Gly-Phe-Met-Thr-Ser-Glu-Lys-Ser-Gln-Thr-Pro-Leu-Val-Thr-Leu-Phe-Lys-Asn-Ala-Ile-Ile-Lys-Asn-Ala-His-Lys-Lys-Gly-Gln | pro-opiomelanocortin (POMC) | morphine | morphiceptin Tyr-D-Ala-Gly-MMe-Phe Gly-ol (DAGO) | naloxonazine β-funaltrexamine naloxone* | guinea-pig ileum |
| | [Met]enkephalin | Tyr-Gly-Gly-Phe-Met | proenkephalin A | | | | |
| δ | [Leu]enkephalin | Tyr-Gly-Gly-Phe-Leu | proenkephalin A | [Leu]enkephalin | D-Ala²-D-Leu⁵enkephalin (DADL) D-Pen²-D-Pen⁵enkephalin | naloxone ICI 154,129 ICI 174,864 | mouse vas deferens guinea-pig ileum |
| κ | dynorphin$_{1-17}$ | Tyr-Gly-Gly-Phe-Leu-Arg-Arg-Ile-Arg-Pro-Lys-Leu Lys-Trp-Asp-Asn-Gln | prodynorphin (proenkephalin B) | ketocyclazocine** | U 50,488 dynorphin$_{1-17}$ | naloxone WIN-44,441-3 MR-2266 | rabbit vas deferens guinea-pig ileum |
| ε | β-endorphin | as above | pro-opiomelanocortin (POMC) | β-endorphin | β-endorphin | naloxone | rat vas deferens guinea-pig ileum |
| σ† | | | | N-allylnormetazocine (SKF 10,047) | phencyclidine | | guinea-pig ileum |

† Sigma receptors may not be exclusively opioid. * *decreasing order of potency of naloxone approximately 1:15:40 for μ:δ:κ (ε potency is between μ and δ).* **Although ketocyclazocine is the prototype benzomorphan agonist, it has been proposed that benzomorphan κ agonists may bind differently than other putative κ agonists.*

ICI 154,129 -N,N-bis-allyl-Tyr-Gly-Gly-ψ-(CH$_2$S)-Phe-Leu-OH ICI 174,864 - N,N-diallyl-Tyr-Aib-Aib-Phe-Leu-OH WIN 44,441-3 - 2a,5a,11S(+)-1-cyclopropyl-5-(1,2,3,4,5,6-hexahydro-8-hydroxy-3,6,11-trimethyl-2,6-methano-3-benzazocin-11-yl)-3-pentanone MR 2266 -(+)-6,11α-diethyl-3-(3-pyridylmethyl)-1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocin-8-ol U 50,488 - trans-(±)-3,4-dichloro-N-methyl-N-(2-(1-pyrrolidinyl)cyclohexyl)-benzeneacetamide




## Effects of opiates: association with receptor subtypes

This chart represents an attempt to integrate three schools of thought regarding the biological identities and functions of multiple opiate receptor subtypes. The accuracy of these estimates of functional specificity is only as precise as the ligands employed and may vary according to experimental conditions. At high doses, most of the ligands indicated in the table above cross-react with other receptor subtypes.

Pasternak and colleagues have suggested that high affinity ($\mu_1$) opiate receptors provide a common binding site for alkaloid and peptide opiates, whereas selectively different effects of opiate ligands may be mediated by separate, low affinity sites (e.g. $\mu_2$, δ, κ and ε). Pert and colleagues have further identified Type I receptors (high affinity, adenylate cyclase-coupled) which may demonstrate fluctuating affinities and interconvert between μ and δ conformations. Type II receptors are fixed in a δ conformation pattern. It is possible that Type I receptors are similar to $\mu_1$ receptors as listed.

It has recently been indicated that μ and δ binding sites may be allosterically coupled or interconvert. Holaday and colleagues have extended the observations to demonstrate functional interactions among κ, μ and δ binding sites.

The effect of opiates on the immune response is an emerging area of investigation and designation of receptor subtypes mediating these responses is very speculative.