Terapia del dolore: la morfina

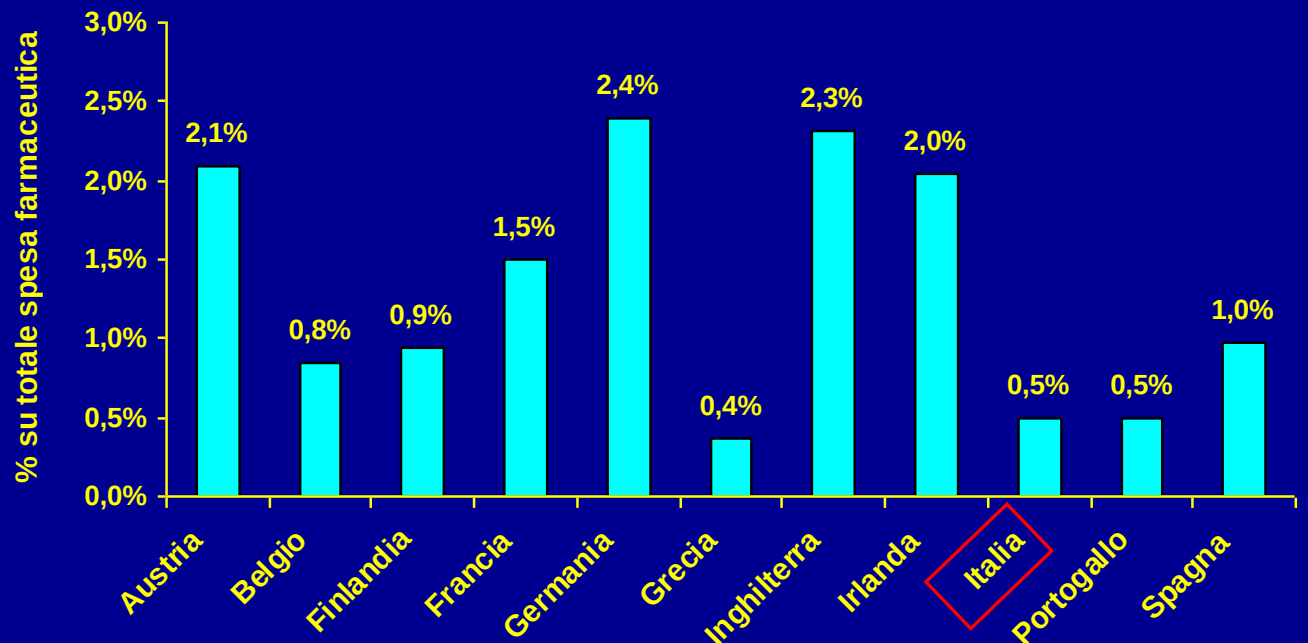
Ogni persona ha il diritto di evitare sofferenze inutili

Il dolore come malattia (sindrome dolorosa)

e non solo sintomo

La morfina è un farmaco e non una droga

Consumo dei farmaci oppioidi in Europa (2004)



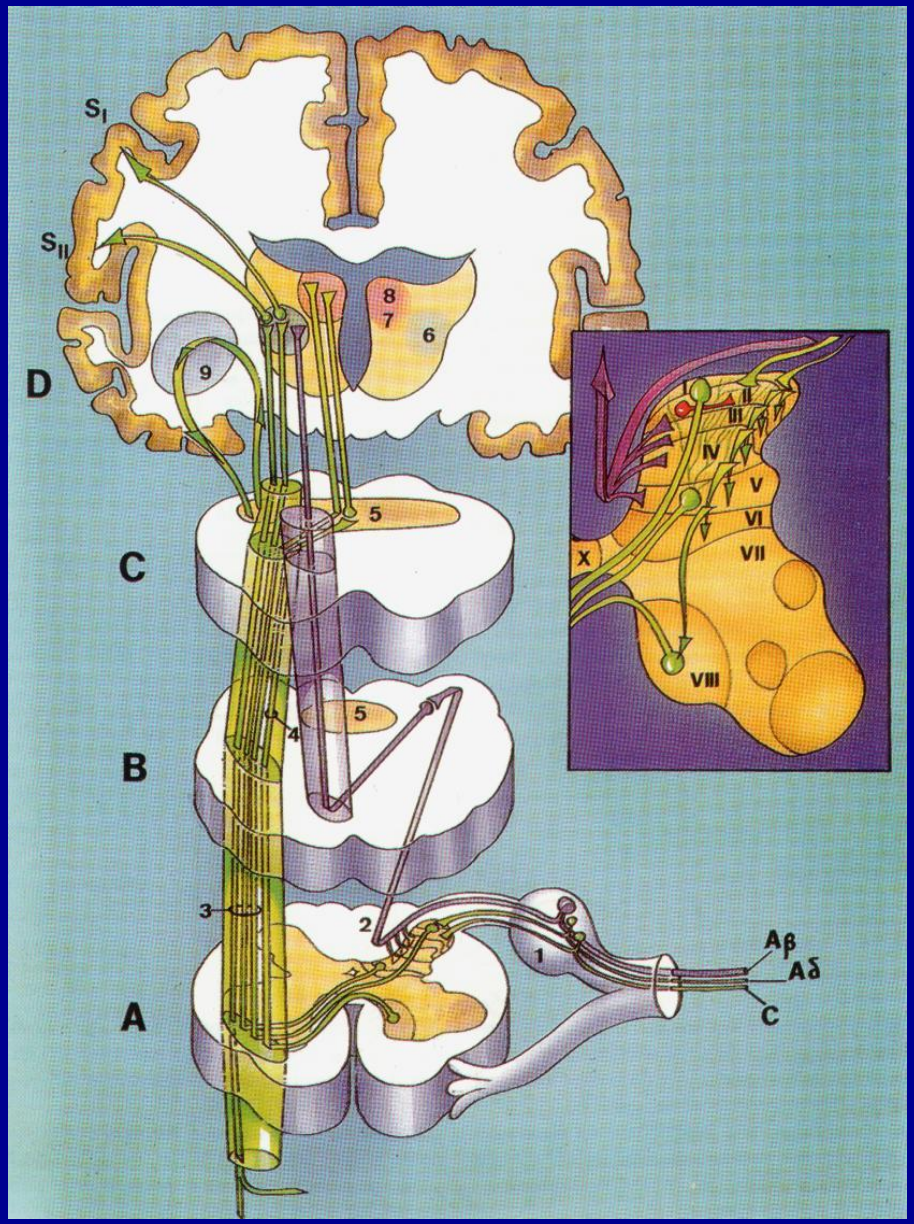
Fonte: elaborazione OsMed su dati IMS

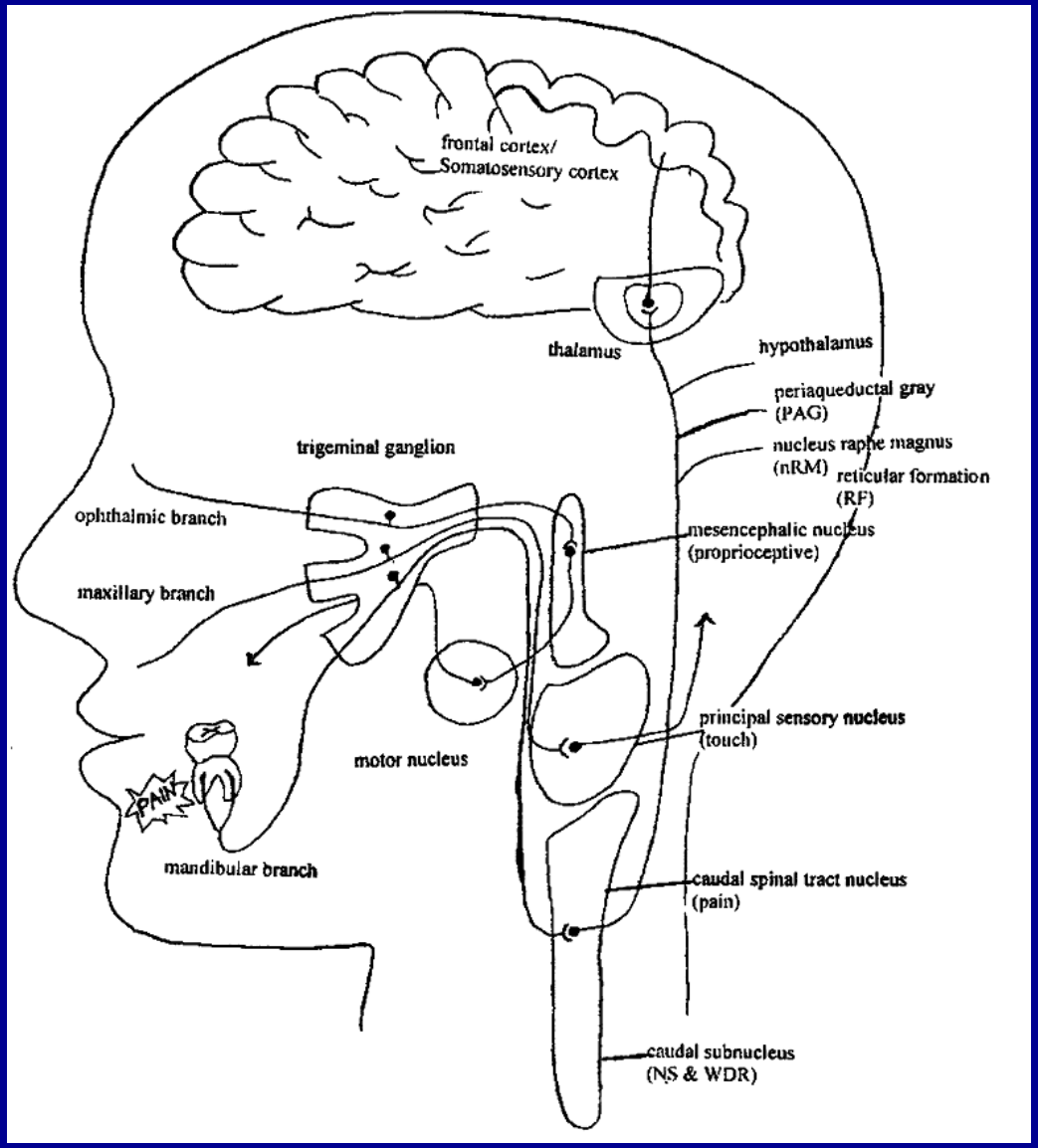
IASP

Il dolore è un’esperienza sensoriale ed emozionale spiacevole associata a danno tissutale, in atto o potenziale, o descritta in termini di danno.

- **Relazione Temporale**
  - *Dolore acuto*
  - *Dolore cronico*
  - *Dolore incidente*
- **Meccanismi fisiopatologici**
  - *Dolore nocicettivo*
    - Somatico
    - Viscerale
  - *Dolore neuropatico*

VIE NOCICETTIVE




frontal cortex/
Somatosensory cortex
thalamus
hypothalamus
periaqueductal gray
(PAG)
nucleus raphe magnus
(nRM)
reticular formation
(RF)
trigeminal ganglion
ophthalmic branch
maxillary branch
mesencephalic nucleus
(proprioceptive)
principal sensory nucleus
(touch)
motor nucleus
PAIN
mandibular branch
caudal spinal tract nucleus
(pain)
caudal subnucleus
(NS & WDR)

Sistemi oppioidi
Terminologia e Storia

Narcotico, oppio, oppiaceo, oppioide (nalossone)

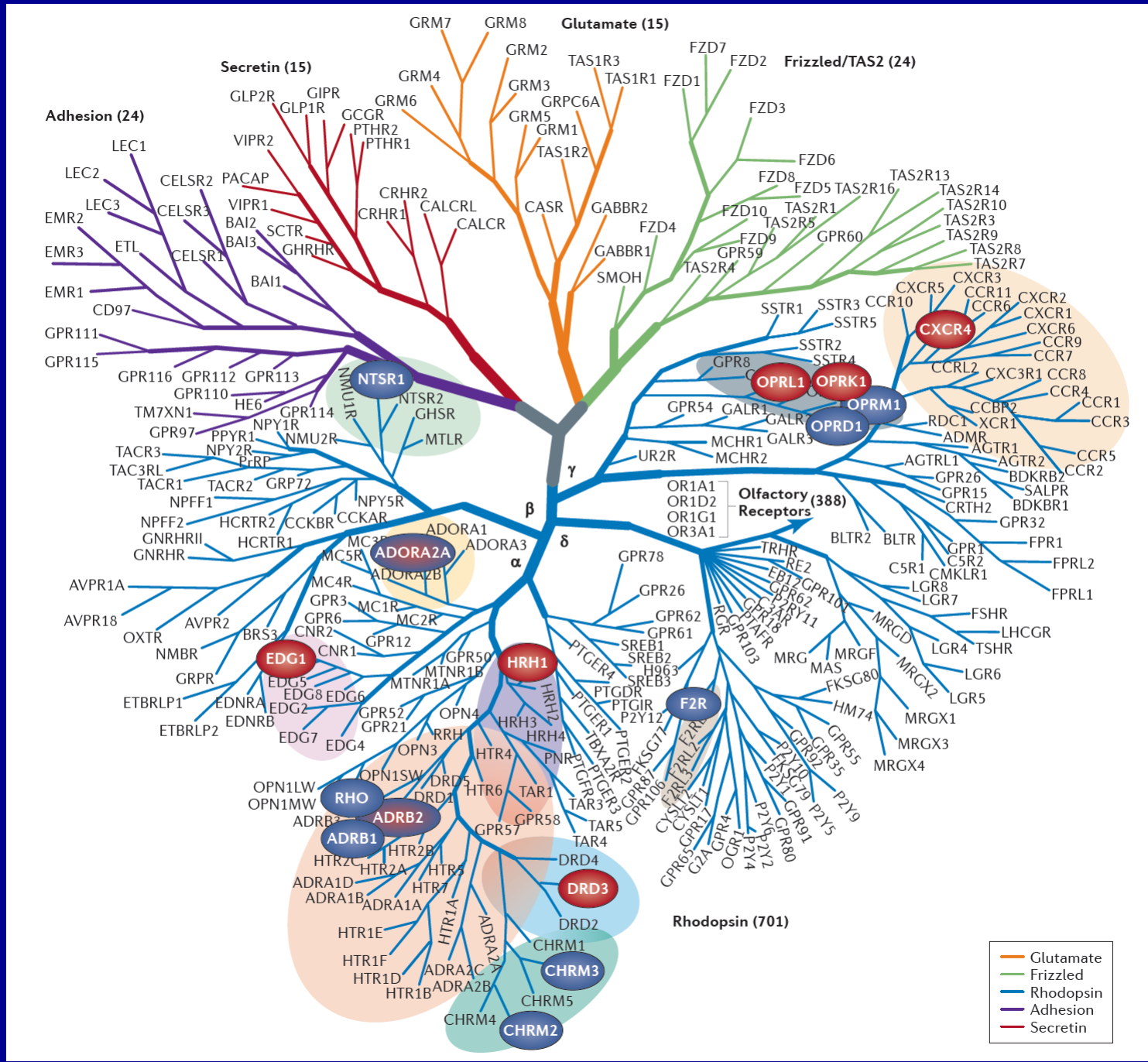
1973 identificazione siti di binding

1973-76 il nalossone reverte l'analgesia indotta da stimolazione elettrica e da stress (SIA)

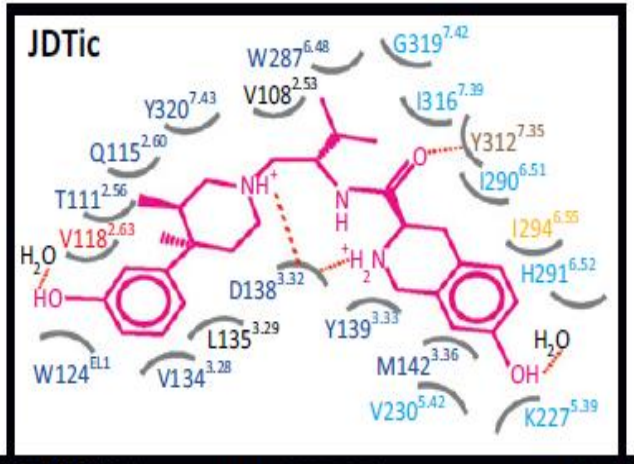
1975 identificazione dei peptidi oppioidi

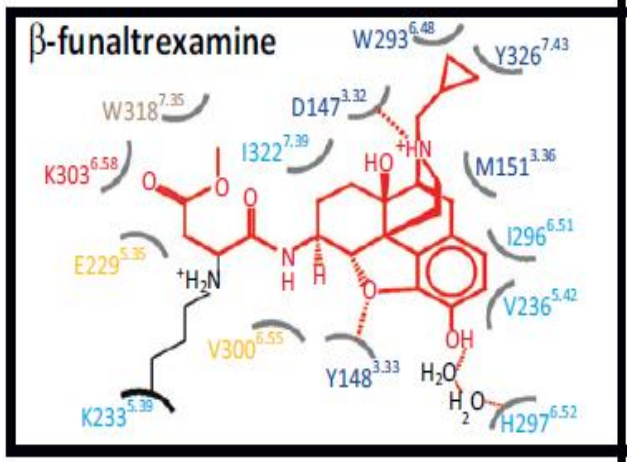
1992-93 cloning delta, kappa e mu

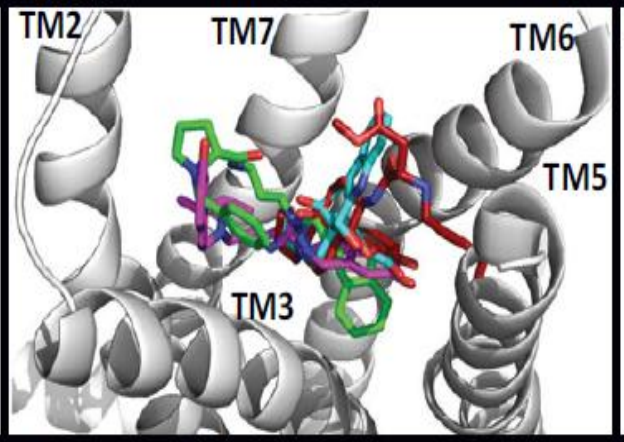
1994-95 NOP e N/OFQ

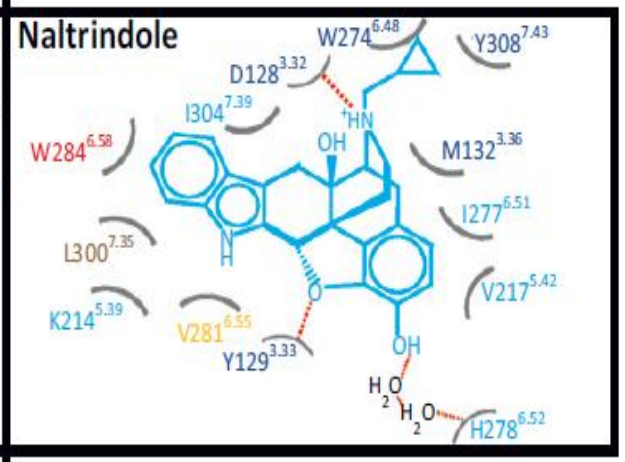

Glutamate (15)
GRM7
GRM8
GRM2
GRM4
GRM3
GRM6
GRM5
GRM1
GRPC6A
TAS1R3
TAS1R1
TAS1R2
CASR
GABBR2
GABBR1
Secretin (15)
GLP2R
GIPR
GLP1R
GCGR
PTHR2
PTHR1
VIPR2
VIPR1
CRHR2
CRHR1
CALCRL
CALCR
PACAP
BAI2
BAI3
SCTR
GHRHR
Adhesion (24)
LEC1
LEC2
LEC3
CELSR2
CELSR3
CELSR1
EMR2
EMR3
EMR1
ETL
CD97
BAI1
GPR111
GPR115
GPR116
GPR112
GPR113
GPR110
HE6
TM7XN1
GPR114
GPR97
Frizzled/TAS2 (24)
FZD7
FZD2
FZD1
FZD3
FZD6
FZD8
FZD5
FZD10
FZD4
FZD9
GPR59
TAS2R4
TAS2R16
TAS2R1
TAS2R5
GPR60
TAS2R13
TAS2R14
TAS2R10
TAS2R3
TAS2R9
TAS2R8
TAS2R7
SMOH
NTSR1
NMU1R
NTSR2
GHSR
MTLR
NPY1R
NMU2R
PPYR1
NPY2R
PrRP
TACR3
TAC3RL
TACR1
TACR2
GRP72
NPFF1
NPFF2
HCRTR2
HCRTR1
CCKBR
CCKAR
NPY5R
GNRHRII
GNRHR
MC3R
MC5R
MC4R
MC1R
MC2R
ADORA1
ADORA3
ADORA2A
ADORA2B
AVPR1A
AVPR18
AVPR2
OXTR
NMBR
GRPR
ETBRLP1
ETBRLP2
BRS3
EDNRA
EDNRB
CNR2
CNR1
GPR3
GPR6
GPR12
EDG1
EDG5
EDG8
EDG6
EDG2
EDG7
EDG4
GPR50
MTNR1B
MTNR1A
GPR52
GPR21
HRH1
OPN4
HRH3
HRH4
RRH
OPN3
HTR4
OPN1SW
OPN1LW
OPN1MW
RHO
ADRB3
ADRB2
ADRB1
DRD5
DRD1
HTR6
TAR1
GPR58
GPR57
TAR4
HTR2B
HTR2C
HTR2A
HTR5
HTR7
ADRA1D
ADRA1B
ADRA1A
DRD4
DRD3
DRD2
HTR1E
HTR1F
HTR1D
HTR1B
HTR1A
ADRA2A
ADRA2C
ADRA2B
CHRM1
CHRM3
CHRM5
CHRM4
CHRM2
α
β
γ
δ
OR1A1
OR1D2
OR1G1
OR3A1
Olfactory Receptors (388)
GPR78
GPR26
GPR62
GPR61
SREB1
SREB2
H963
SREB3
PTGDR
PTGIR
P2Y12
F2R
PTGER4
PTGER1
TBXA2R
PTGER2
PKSG17
GPR87
GPR106
F2RL2
F2RL3
CYSLT2
CYSLT1
GPR17
GPR65
G2A
GPR4
OGR1
P2Y6
P2Y2
P2Y4
GPR80
GPR91
P2Y1
P2Y10
P2Y11
GPR92
GPR35
GPR55
P2Y9
P2Y5
TRHR
RE2
EB12
GPR62
GPR101
GPR87
GPR18
GPR103
RGR
OPTAFR
MRG
MRGF
MAS
FKSG80
HM74
MRGX1
MRGX3
MRGX4
MRGX2
MRGD
LGR4
LGR5
LGR6
TSHR
FSHR
LHCGR
LGR8
LGR7
BLTR2
BLTR
C5R1
GPR1
C5R2
CMKLR1
FPR1
FPRL2
FPRL1
GPR32
TRHR
GPR26
GPR15
CRTH2
BDKRB1
BDKRB2
SALPR
AGTR1
AGTR2
AGTRL1
CCR5
CCR2
CCBP2
RDC1
XCR1
CCR1
CCR3
CCR4
CXC3R1
CCR8
CCRL2
CCR7
CCR9
CXCR6
CXCR1
CXCR2
CCR6
CCR11
CXCR3
CXCR5
CCR10
CXCR4
SSTR1
SSTR3
SSTR5
SSTR2
SSTR4
GPR8
OPRL1
OPRK1
OPRM1
OPRD1
GPR54
GALR1
GALR2
GALR3
MCHR1
MCHR2
UR2R
ADMR
Rhodopsin (701)
Glutamate
Frizzled
Rhodopsin
Adhesion
Secretin

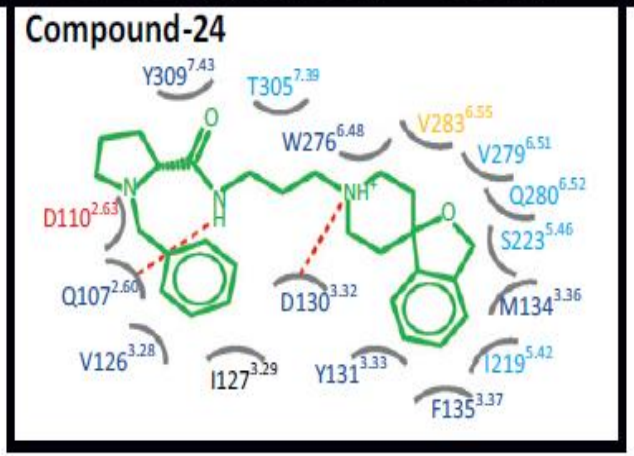

nature
WHERE OPIATES HIT HOME
Crystal structures for the four major opioid receptor subgroups
LAST CHANCE TO SEE
A HELPING HAND
IN A DOG FIGHT

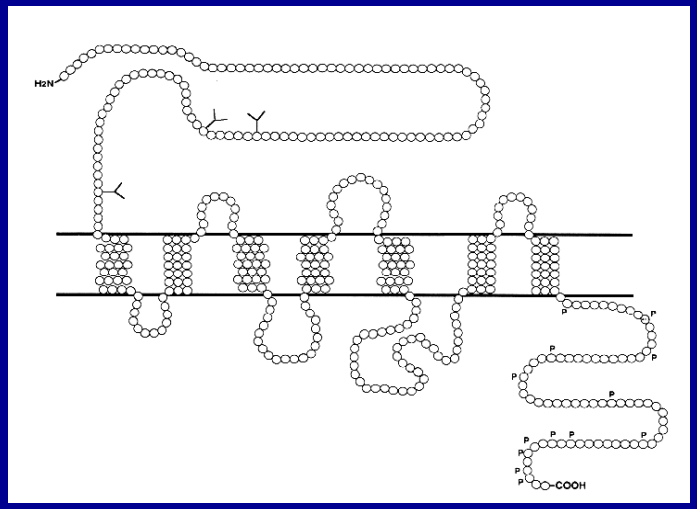

JDTic
W287 6.48
G319 7.42
V108 2.53
Y320 7.43
I316 7.39
Q115 2.60
Y312 7.35
I290 6.51
T111 2.56
I294 6.55
V118 2.63
H291 6.52
D138 3.32
L135 3.29
Y139 3.33
W124 EL1
V134 3.28
M142 3.36
V230 5.42
K227 5.39


β-funaltrexamine
W293 6.48
Y326 7.43
W318 7.35
D147 3.32
K303 6.58
I322 7.39
M151 3.36
I296 6.51
E229 5.35
V236 5.42
V300 6.55
Y148 3.33
K233 5.39
H297 6.52


TM2
TM7
TM6
TM5
TM3


Naltrindole
W274 6.48
Y308 7.43
D128 3.32
I304 7.39
W284 6.58
M132 3.36
I277 6.51
L300 7.35
V217 5.42
K214 5.39
V281 6.55
Y129 3.33
H278 6.52

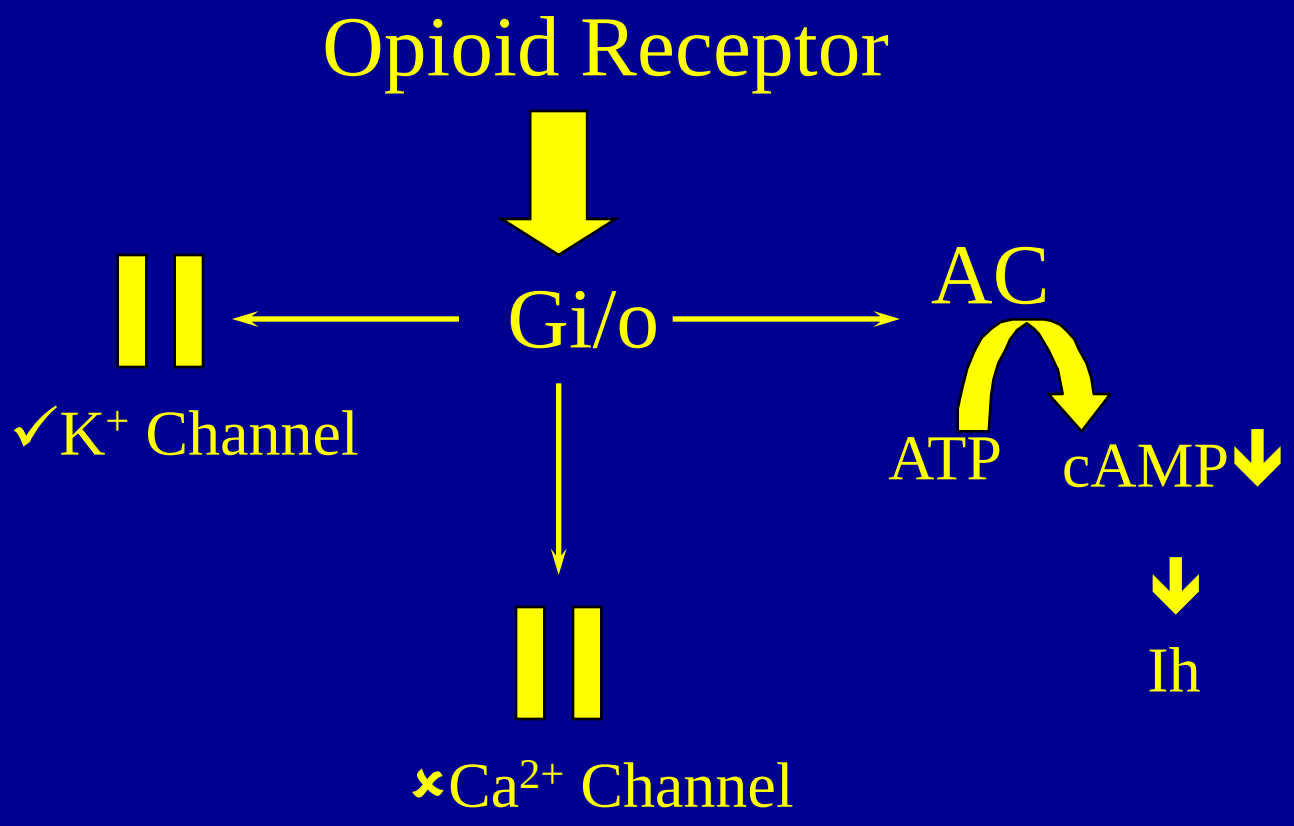

Compound-24
Y309 7.43
T305 7.39
V283 6.55
W276 6.48
V279 6.51
Q280 6.52
D110 2.63
S223 5.46
Q107 2.60
D130 3.32
M134 3.36
V126 3.28
I127 3.29
Y131 3.33
I219 5.42
F135 3.37



Opioid Receptors

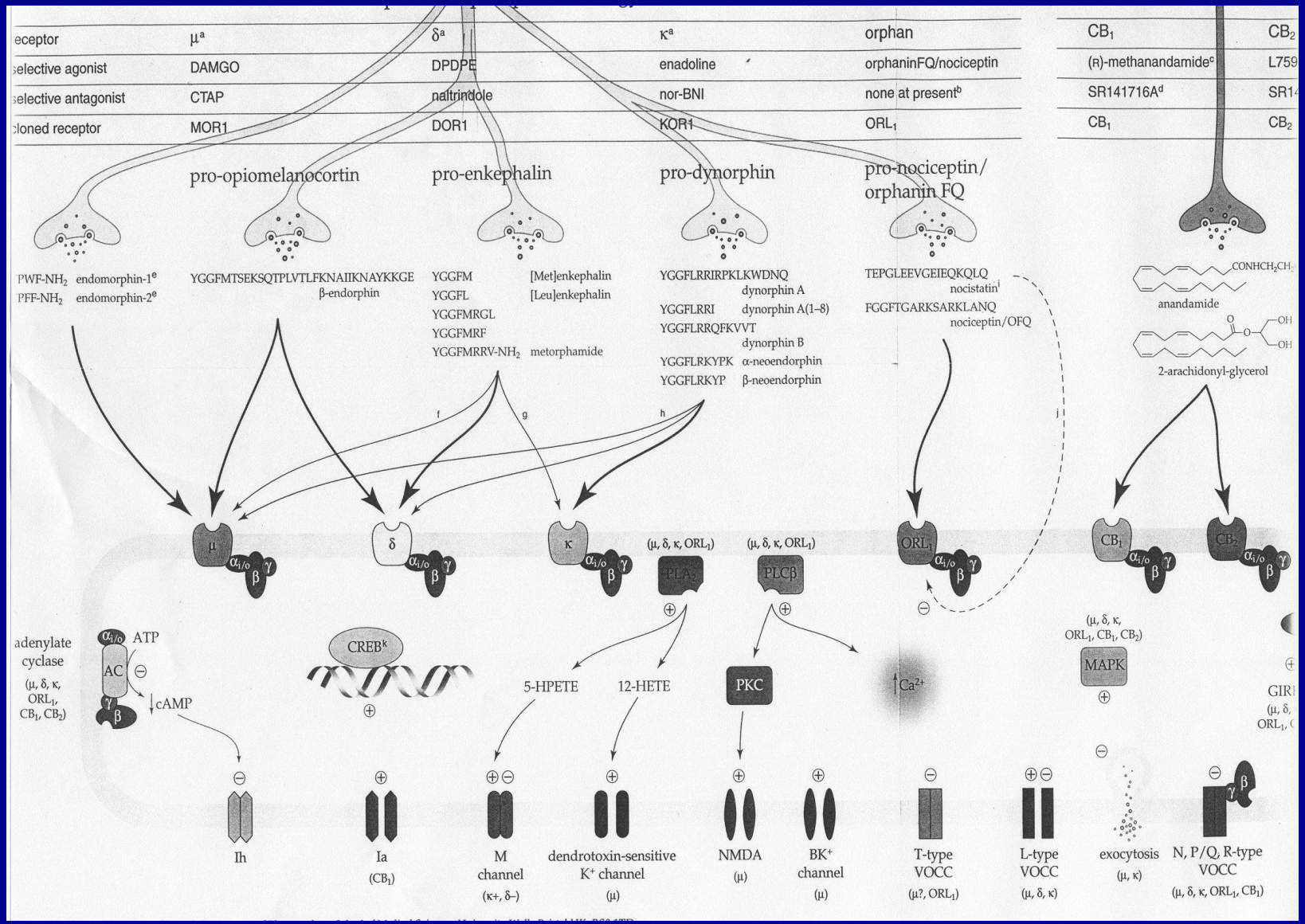
- Opioids interact with specific receptors
- Three primary subtypes:
  - μ, δ and κ
  - Subtypes: μ1-3, δ1-2, κ1-3
- G-protein coupled
  - Close voltage sensitive Ca^{2+} channels
  - Open K^{+} channels to hyperpolarise
  - Inhibit cAMP formation

Signal Transduction-simplified



AC=Adenylyl cyclase. Gi/Go are pertussis toxin sensitive

Signal Transduction

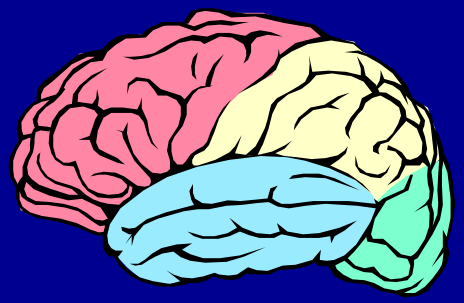


Opioid Receptor Classification and Reclassification.

<1992	1992-1996	1996 (IUPHAR)	2000 (IUPHAR)
μ (1-3)	μ_1 (MOR1/B)	OP_3	MOP-μ
δ (1,2)	δ_2 (DOR)	OP_1	DOP-δ
κ (1-3)	κ_1 (KOR)	OP_2	KOP-κ
--	ORL1/LC132	OP_4	NOP

μ, δ and κ Opioid Receptor Location-CNS

- Many brain areas including:
  - Cortex
  - Hippocampus
  - PAG,NRM and LC
  - Thalamus, hypothalamus
  - Brainstem
- Spinal cord



Opioid Receptor Location-Periphery

- Vas deferens (δ)
- Myenteric plexus (μ)
- Lymphocytes/thymocytes (μ?)
- Heart (μ, δ and κ)
- Knee joints (?)

Basic Pharmacology

Receptor ligand	Select. agonist	Select. Antagonist	Clinical
μ	DAMGO	CTOP	Mor, Fent
δ	DPDPE	Naltrindole	None
κ	spiradoline	NorBNI	None

DAMGO	[D-Ala^2,Me-Phe^{4}Gly-ol]-enkephalin
DPDPE	[D-Pen^{2,5}]-enkephalin
CTOP	D-Phe-Sys-Tyr-D-Trp-Orn-Thr-Pen-Thr NH_2
NorBNI	nor-binaltorphimine

Endogenous opioids

β-Endorphin (31aa)

Tyr-Gly-Gly-Phe-Met-Thr-Ser-Glu-Lys-Ser-Gln-Thr-Pro-Leu-Val-Thr-Leu-Phe-Lys-Asn-Ala-Ile-Val-Lys-Asn-Ala-His-Lys-Lys-Gly-Gly

met-Enkephalin (5aa)

Tyr-Gly-Gly-Phe-Met

Dynorphin (17aa)

Tyr-Gly-Gly-Phe-Leu-Arg-Arg-Ile-Arg-Pro-Lys-Leu-Lys-Trp-Asp-Asn-Gln

Selectivity !!!

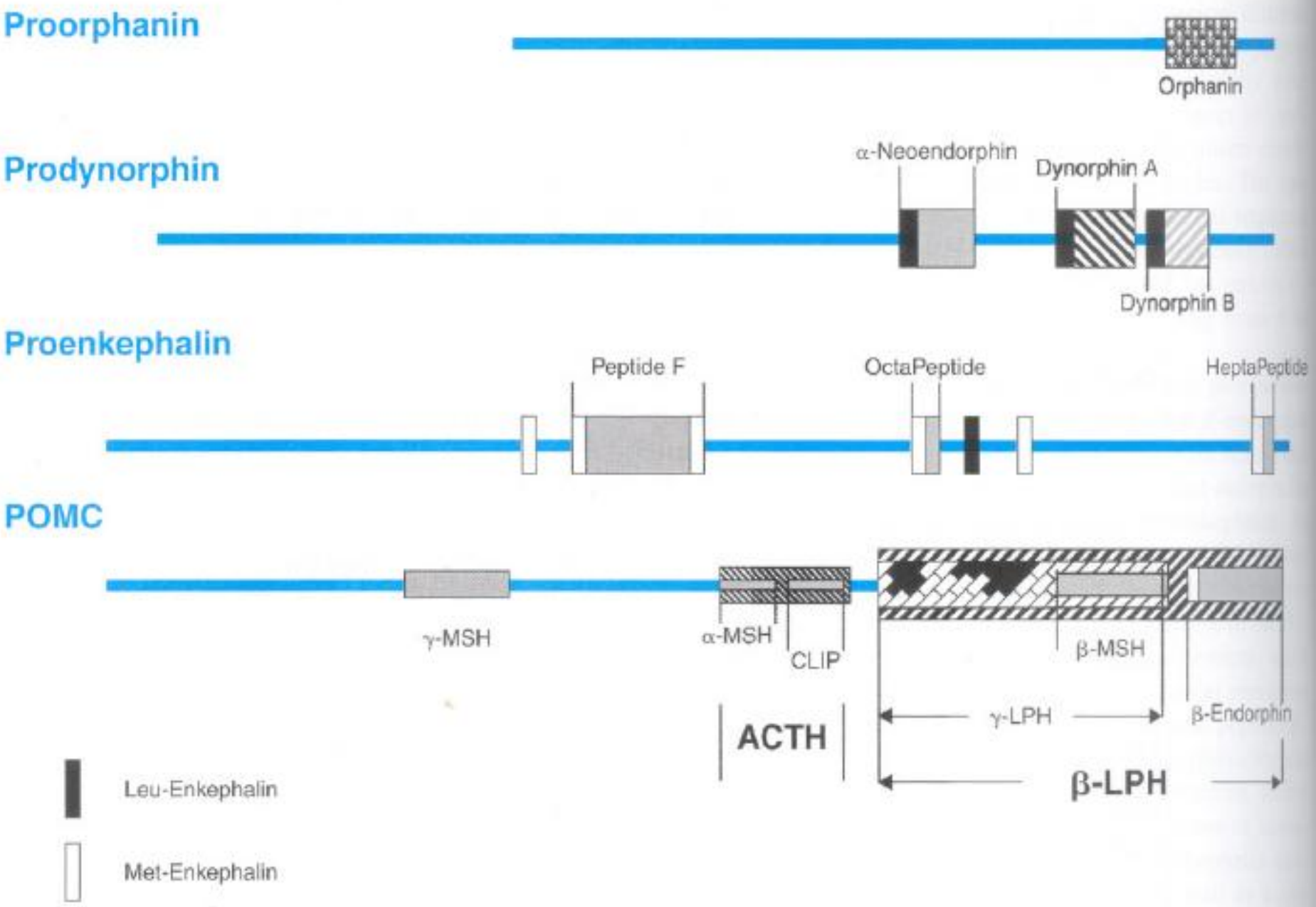


Figure 23–1. Peptide precursors. *(From Akil* et al., *1998.)*
POMC, proopiomelanocortin; ACTH, adrenocorticotropic hormone; β-LPH, β-lipotropin.

Endomorphins

- Zadina et al Nature 1997
- Isolated two endogenous peptides for the μ receptor completing the story that began in the 70's
- Very high affinity and **selectivity**
- Endomorphin-1 Tyr-Pro-Trp-Phe-NH_2
- Endomorphin-2 Tyr-Pro-Phe-Phe-HN_2

- Clinical potential to be explored
- Precursor ???

EFFETTI CENTRALI DELLA MORFINA

ANALGESIA

- dose dipendente
- no effetto tetto
- tolleranza, dipendenza fisica

- sedazione - agitazione psicomotoria
- miosi
- nausea, vomito (ctz)
- manifestazioni psicoaffettive
- rigidita'-mioclonie-tremori
- depressione respiratoria
- broncospasmo (Ist??)
- depressione della tosse

EFFETTI PERIFERICI DELLA MORFINA

✓EFFETTI CARDIOVASCOLARI

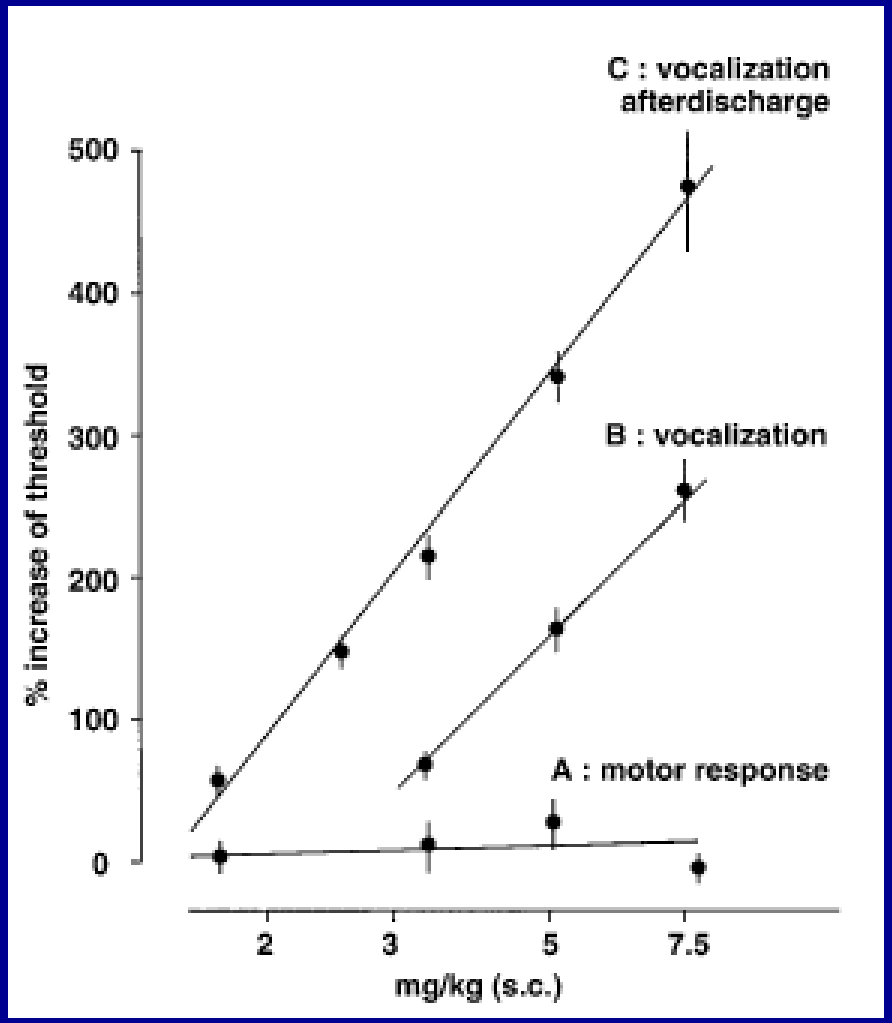
Riduzione consumo ossigeno cardiaco
Ipotensione (IST?)

✓EFFETTI GASTROINTESTINALI

Diminuzione secrezioni e motilità propulsiva
Aumento tono sfinteri → stipsi
Ipertensione vie biliari

✓EFFETTI SULL'APPARATO URINARIO

Contrazione della diuresi
Effetti inibitori sul detrusore


C : vocalization
afterdischarge
B : vocalization
A : motor response
% increase of threshold
500
400
300
200
100
0
2
3
5
7.5
mg/kg (s.c.)

MOP(-/-) mice

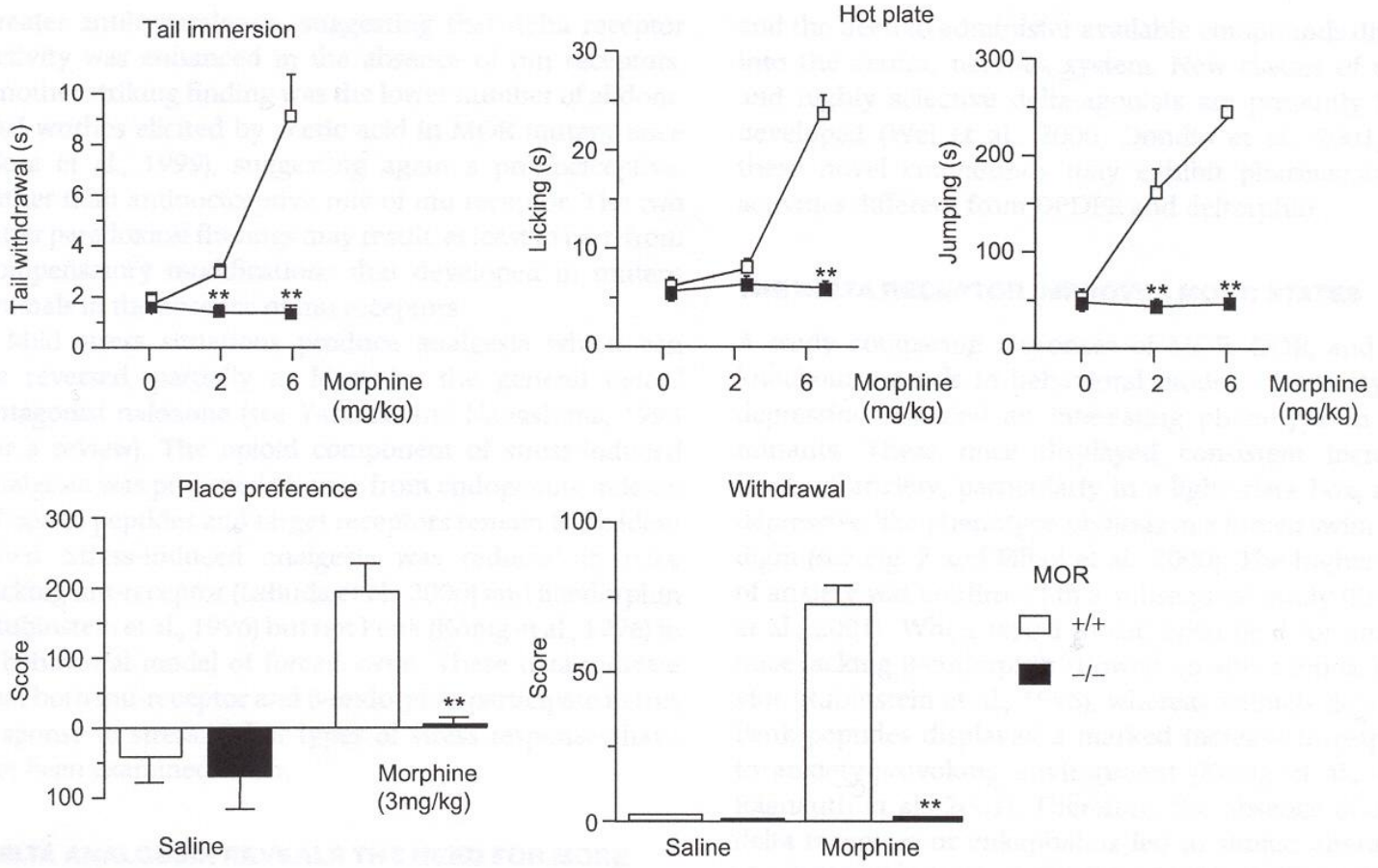


Fig. 1 Responses to morphine are abolished in MOR-deficient mice. Morphine analgesia was measured in the tail immersion and hot plate tests (Top panels). Antinociceptive responses are shown as latencies (seconds). Morphine reward was examined in a conditioned place preference assay (bottom left panel). Place preference is expressed as the difference between time spent in saline- or morphine-associated compartments after conditioning (score). Physical dependence to morphine was evaluated based on withdrawal signs (bottom right panel). Mice were exposed to increasing doses of morphine during six days, followed by a single administration of the opioid antagonist naloxone. Naloxone-precipitated withdrawal is expressed as a global score accounting for eight withdrawal signs. Black stars indicate statistical differences between wild-type and MOR-mutant mice; $*P < 0.05$, $**P < 0.01$. In all the experiments morphine was ineffective in the MOR knockout mice. Data are from Ref (Matthes et al., 1996).

Scala del dolore OMS

1	2	3	4	5	6	7	8	9	10
lieve (I grado)				moderato (II grado)		severo (III grado)			

III grado

morfina, ossicodone, buprenorfina, fentanil

Oppioidi forti ± paracetamolo o FANS ± adiuvanti

II grado

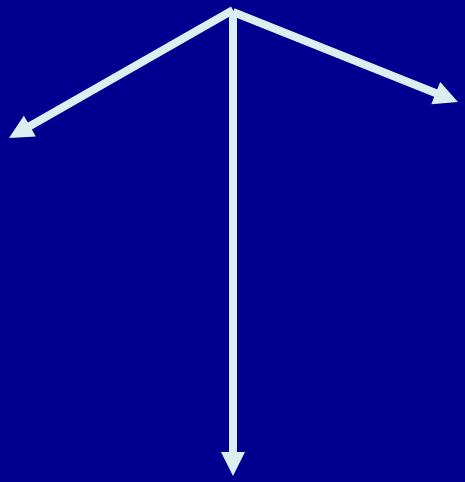
tramadolo codeina+paracetamolo, ossicodone+paracetamolo

Oppioidi deboli ± paracetamolo o FANS ± adiuvanti

I grado

Paracetamolo o FANS ±adiuvanti

adiuvanti



- Effetto analgesico diretto
- antidepressivi
- anticonvulsivanti
- anestetici locali
- corticosteroidi
- bifosfonati

Azione contrastante gli effetti collaterali:

antiemetici
lassativi

- Effetto analgesico indiretto:
- antispastici
- antitussigeni
- miorilasanti
- ansiolitici
- antidepressivi

Vie di somministrazione morfina e oppioidi

Orale: **morfina formulazione pronta o a lento rilascio**

Buccale: **fentanyl oralet ⇒ dolore incidente**

Sublinguale???

Intranasale???

Rettale

Transdermica: **fentanyl, buprenorfina**

Sottocutanea: **morfina boli ripetuti o infusione continua *non effetti "picchi e valli"***

Endovenosa: **morfina boli ripetuti o infusione continua**

MORFINA PER OS

ONSET TIME <60min

quantità maggiore di M6G
ricircolo entero epatico ed efficacia della via orale

MORFINA ad azione pronta → **FASE DI ADATTAMENTO CONTROLLO RIESACERBAZIONI**

durata effetto:4 ore
rivalutazione dose giornaliera dopo 24-48h

PREPARATI COMMERCIALI
MORFINA solfato ad azione PRONTA

ORAMORPH®

Soluzione orale (gocce)
sciroppo

MORFINA solfato a RILASCIO GRADUALE

mantenimento
picco plasmatico 2-4h;secondo picco 4-6h
durata effetto: 8-12h
somministrazione ogni 8-12 h

compresse → **SKENAN®**

MS CONTIN®

VIE ALTERNATIVE DI SOMMINISTRAZIONE DELLA MORFINA NEL DOLORE CRONICO

VIA SOTTOCUTANEA

Picco plasmatico 15-30 min; ONSET TIME 5-15 min

Bolo od Infusione continua (PCA)
Dosaggio-efficacia paragonabile s.c.-e.v.

VIA ENDOVENOSA

Cateteri venosi a permanenza

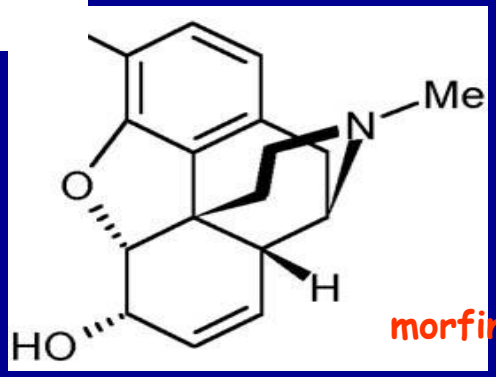
Impossibilità di utilizzo via sottocutanea

TAVOLA CONVERSIONE MORFINA

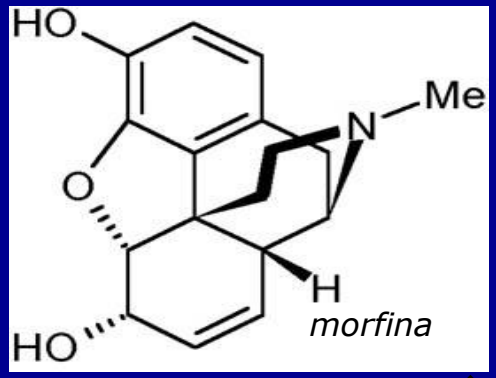
- 300 mg. X os
- 100 mg EV (1/3)
- 10 mg peridurale (1/30)
- 1 mg intratecale (1/300)

glucuronide-O

GLUCURONIL TRANSFERASI

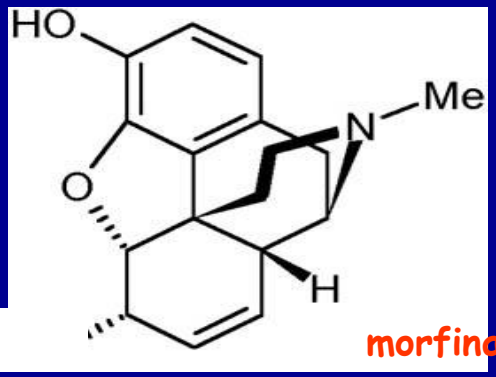


morfina-3-glucuronide



morfina

GLUCURONIL TRANSFERASI



glucuronide-O

morfina-6-glucuronide

Metabolita attivo

Rotazione degli oppioidi

Accettata nella pratica clinica, anche se non si conoscono gli specifici meccanismi

All'equilibrio:

↑ efficacia

↓ Effetti collaterali

Farmaco:

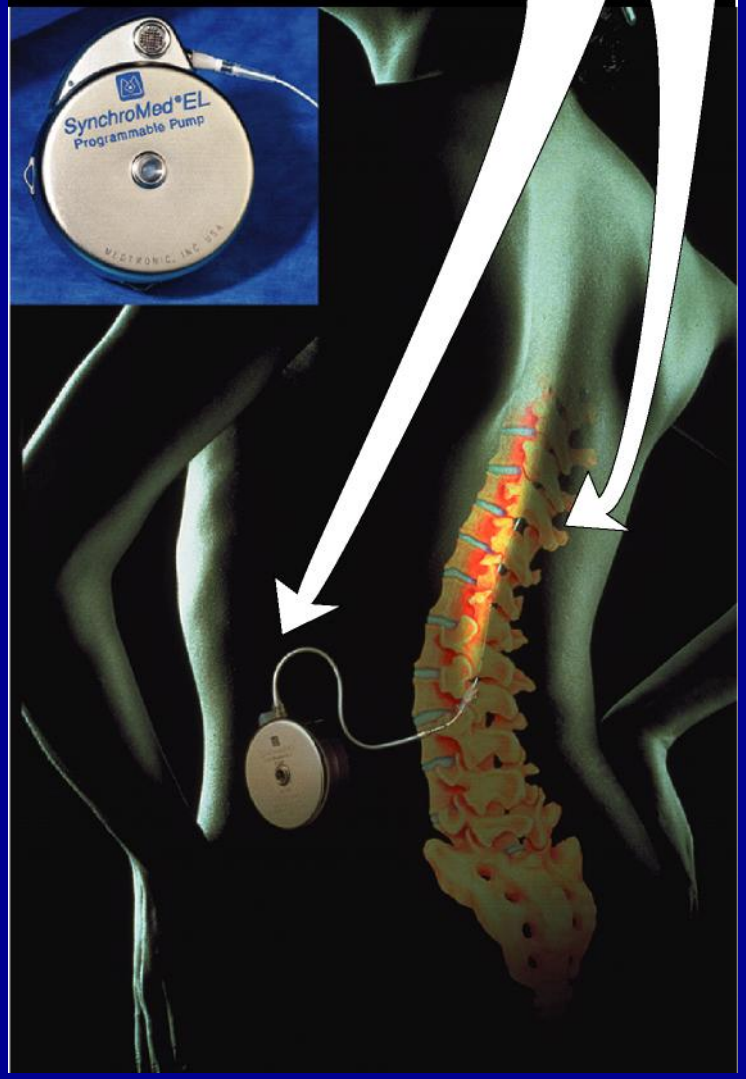
- morfina
- idromorfone
- fentanyl
- ossicodone

Via:

-orale
- transdermica
-endovena
- sottocute 5%

Journal of Pain and Symptom Management Vol. 38 No. 3 September 2009
2010 World Institute of Pain, Pain Practice, 2010

La pompa è impiantata all'interno della cute. Un catetere che si stacca dalla pompa è posto all'interno dello spazio del liquido spinale. La velocità della pompa può essere controllata da un dispositivo esterno di telemetria.



Effetti collaterali piu' frequenti

sonnolenza, confusione, nausea, vertigini, stipsi, vomito

Altri effetti collaterali

depressione respiratoria:

- Correlata alla dose e via di somministrazione
- Meno marcata nei pazienti con dolore

ritenzione urinaria, prurito

Tolleranza e Dipendenza

meno importante per oppioide per os a lunga durata d'azione es. morfina lento rilascio, metadone, oxicodone lento rilascio

Tolleranza e dipendenza non implicano "abuso"

non associato all'uso terapeutico

Joranson et al., JAMA, 2000

Controindicazioni

Dolore non diagnosticato

Dolore ricorrente (es. cefalea)

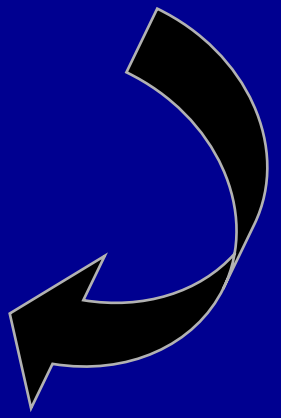
Trauma cranico (↑press. endocranica)

Colica biliare (↑press. Biliare)


Controindicazione assoluta per la *meperidina* e controindicazione relativa per gli altri analgesici oppiacei a causa della elevata incidenza di coma iperpiressico.
Aumento della depressione del SNC, particolarmente della depressione respiratoria.
Inibitori della MAO
Sedativo-ipnotici
Analgesici oppiacei
Antidepressivi triciclici
Antipsicotici
Aumento della sedazione; effetti variabili sulla depressione respiratoria.

Intossicazione acuta

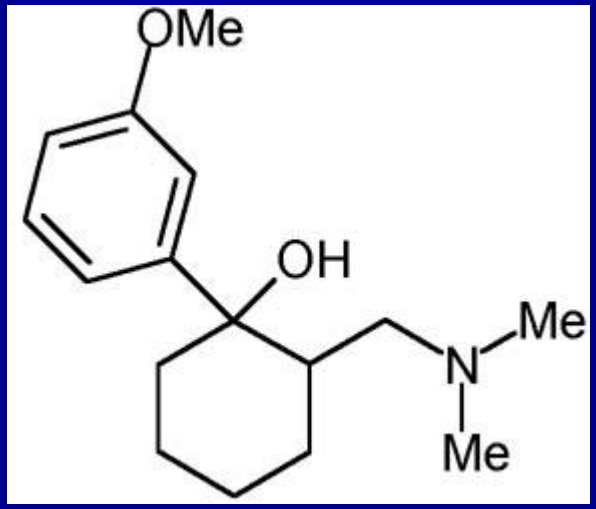
Frequenza respiratoria ridotta (2-3 atti al minuto)
Miosi
Sedazione…..coma
Ipotensione progressiva…..shock
Ipotermia, ipotono muscolare, anuria



NALOXONE

Narcan®

Tramadolo



Derivato della codeina

E' un agonista oppioide poco potente che inibisce la ricaptazione di NA e 5-HT favorendo cosi analgesia spinale

Scarsa propensione alla tolleranza e dipendenza (no ricetta stupefacenti)

Tramadolo

Minor propensione ad inibire centro respiro

Buona biodisponibilita' per os

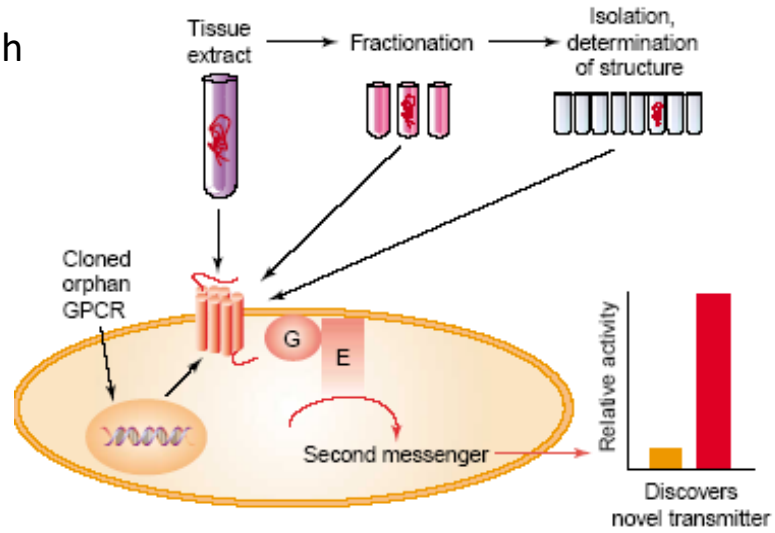
50-100 mg ogni 6h (max 400 mg die)

Trattamento di dolori acuti e cronici come pure di dolori indotti da interventi chirurgici e diagnostici. Il tramadolo è usato per trattare il dolore da moderato a severo e la maggior parte delle nevralgie inclusa la nevralgia trigeminale

The N/OFQ – NOP receptor system

Opioid receptor-like 1 (NOP)

- ✓GPCR
- ✓ High structural homology with classical opioid receptors
- ✓ No affinity for opioid ligands



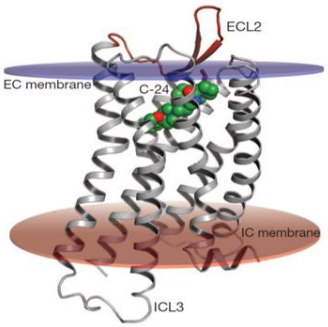
1995: identification of the natural ligand

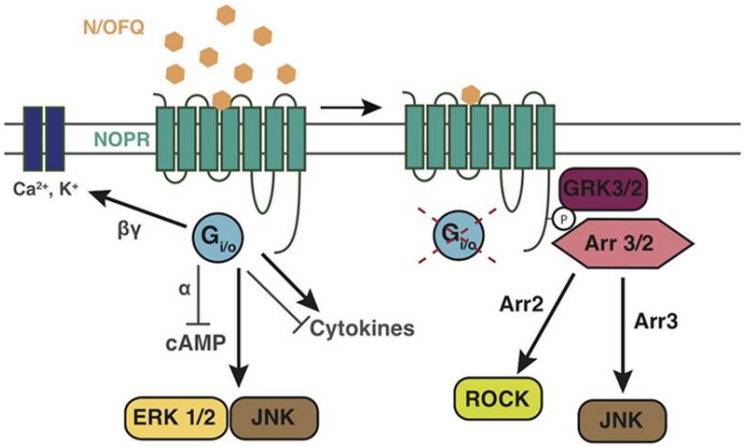
Meunier et al., Nature, 1995
Reinschied et al., Science, 1995

Nociceptin/Orphanin FQ (N/OFQ)

FGGFTGARKSARKLANQ

- ✓High structural homology with dynorphin A
- ✓ No affinity for opioid receptors





The nociceptin/orphanin FQ receptor: a target with broad therapeutic potential

David G. Lambert

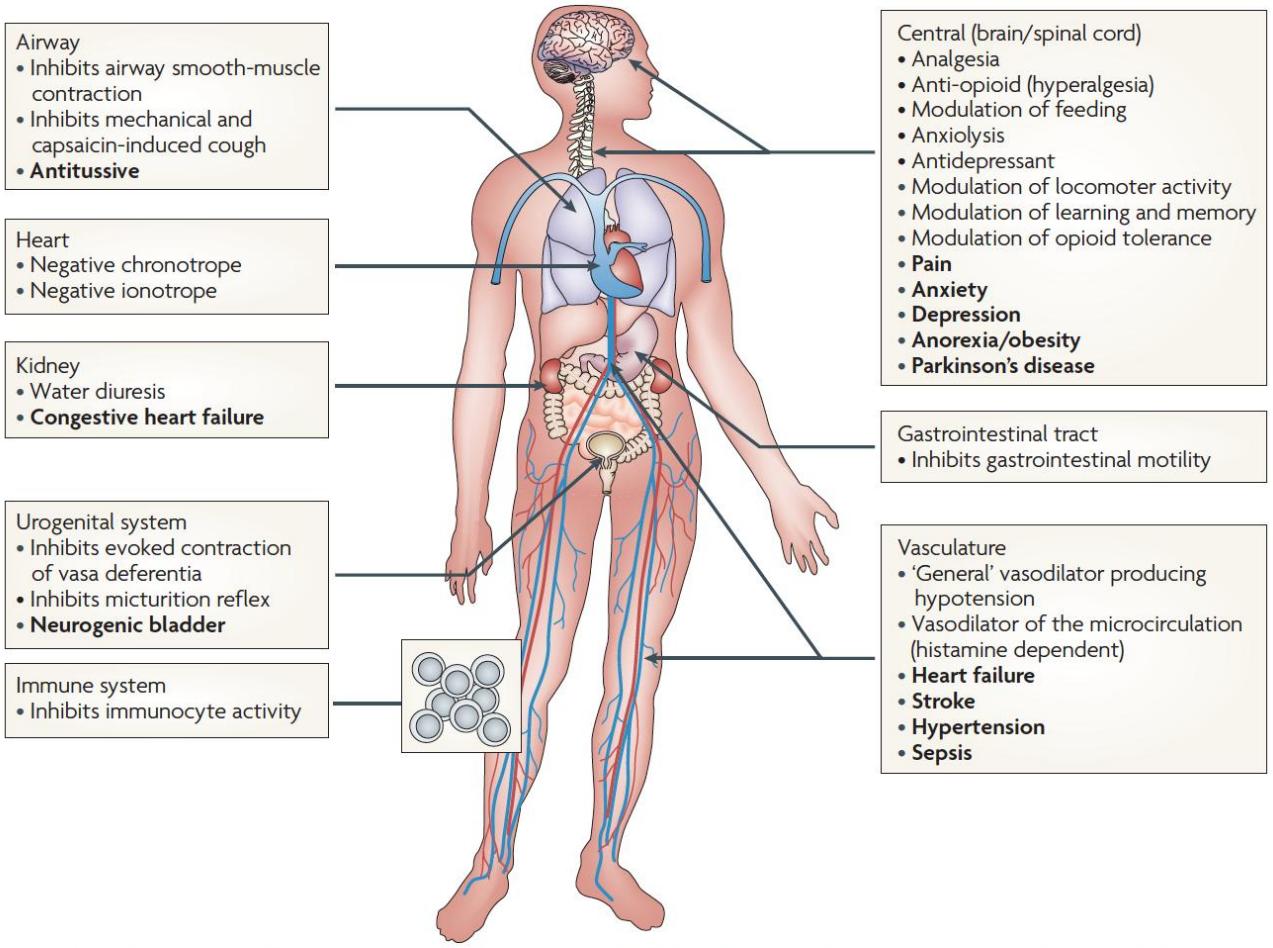
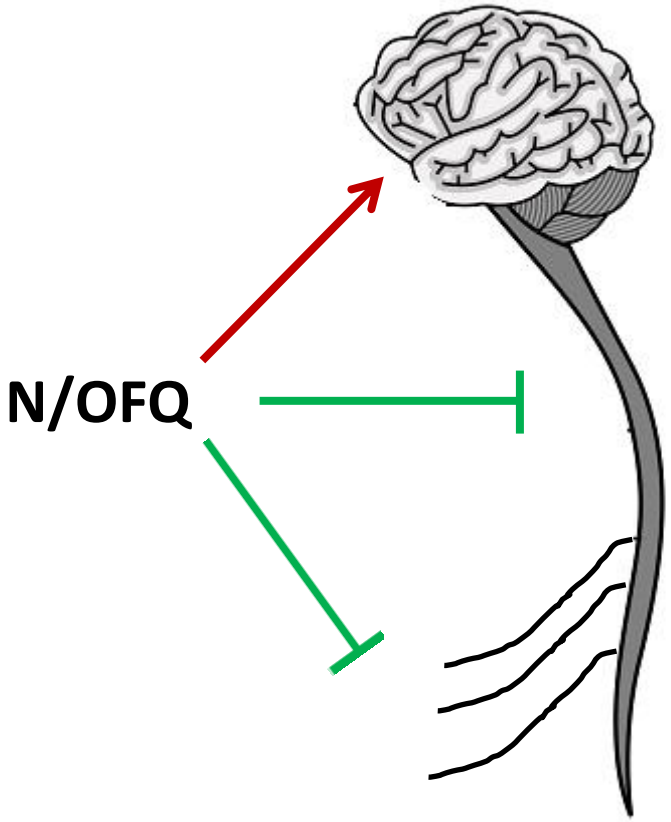
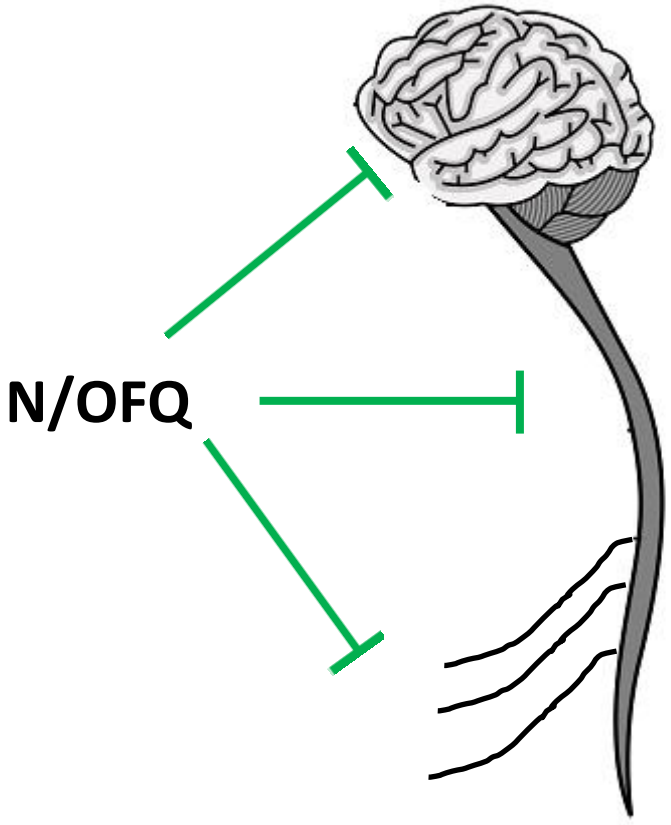


Figure 1 | **Pleiotropic effects of nociceptin/orphanin FQ (N/OFQ) on major organ systems.** Potential clinical indications are noted in bold.

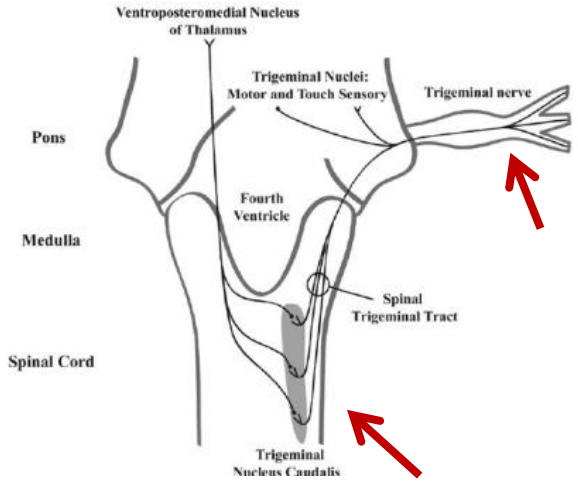
The N/OFQ – NOP receptor system and pain



The N/OFQ – NOP receptor system and pain



The N/OFQ – NOP receptor system in the trigeminal territory



- ❑ N/OFQ and NOP in the trigeminal ganglion and spinal caudalis nucleus
- ❑ N/OFQ co-localized with SP and CGRP

(Xie et al. 1999; Hou et al. 2003; Neal et al. 1999a; Neal et al. 1999b, Witta et al. 2004)

Nociceptin (1–13)NH_2 inhibits stimulated calcitonin-gene-related-peptide release from primary cultures of rat trigeminal ganglia neurones

A Capuano[1,2], D Currò[2], C Dello Russo[2], G Tringali[2], G Pozzoli[2], G Di Trapani[1] & P Navarra[2]
[1]*Department of Neuroscience and* [2]*Institute of Pharmacology, Catholic University Medical School, Rome, Italy*

Journal of Physiology (2001), **536.1**, *pp.*35–47

Nociceptin inhibits calcium channel currents in a subpopulation of small nociceptive trigeminal ganglion neurons in mouse

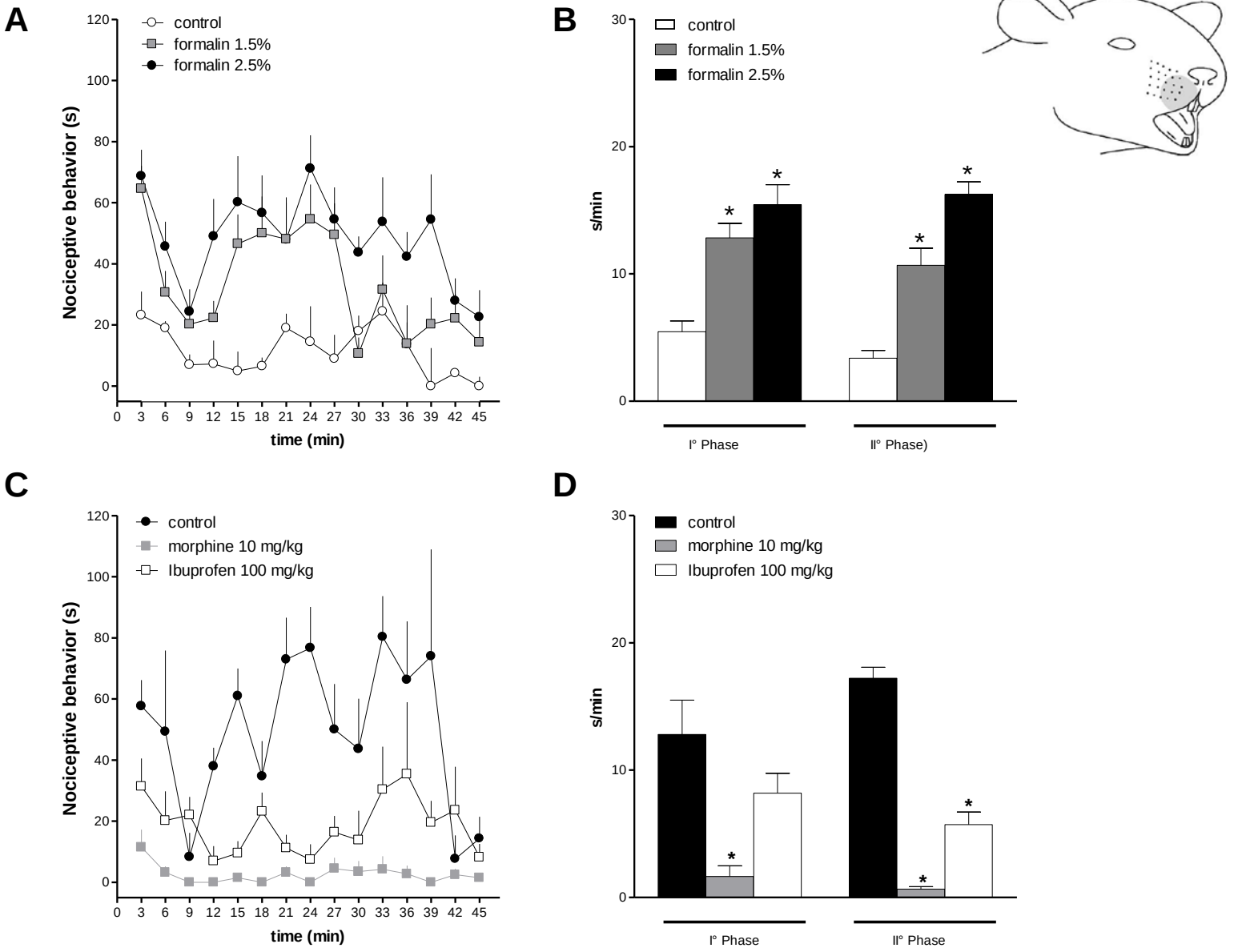
Stephanie L. Borgland, Mark Connor and MacDonald J. Christie *

ORPHANIN FQ (NOCICEPTIN) MODULATES RESPONSES OF TRIGEMINAL NEURONS EVOKED BY EXCITATORY AMINO ACIDS AND SOMATOSENSORY STIMULI, AND BLOCKS THE SUBSTANCE P-INDUCED FACILITATION OF *N*-METHYL-D-ASPARTATE-EVOKED RESPONSES

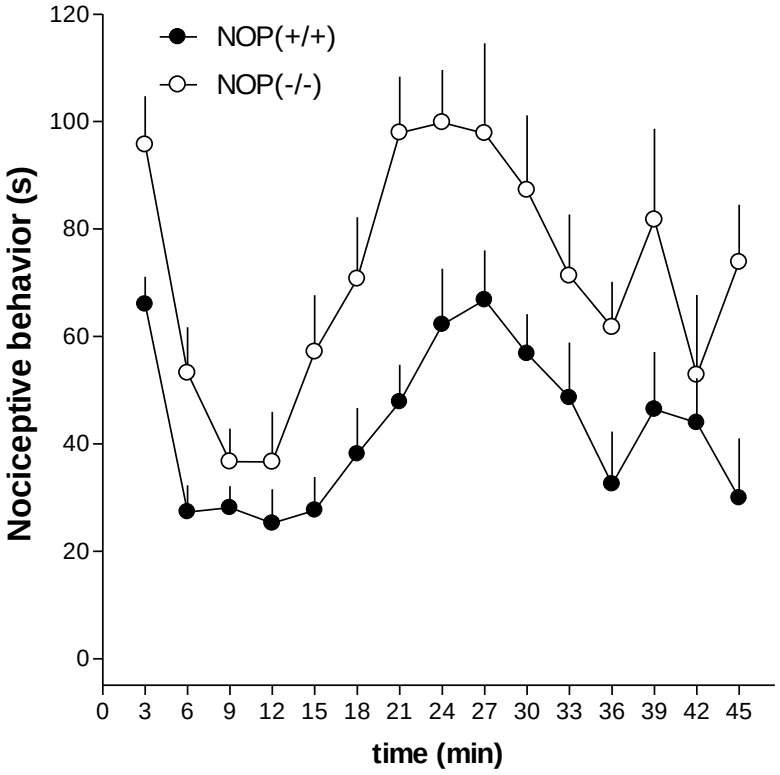
X.-M. WANG, K.-M. ZHANG, L. O. LONG and S. S. MOKHA*
Department of Anatomy and Physiology, Meharry Medical College, 1005 D.B. Todd Boulevard, Nashville TN 37208, U.S.A.

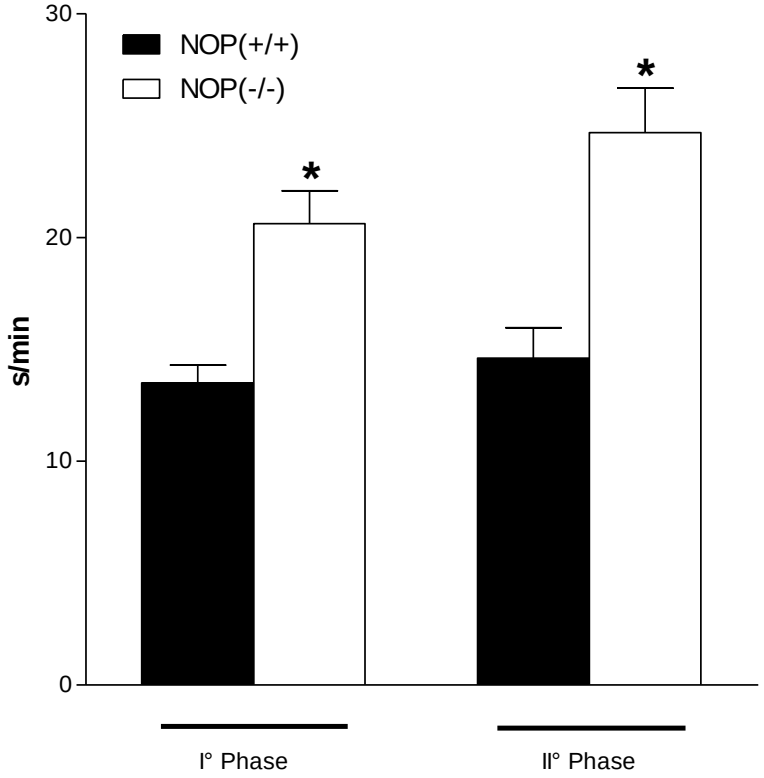
- ❑ In these structures N/OFQ evokes inhibitory effects

OFF test – set up



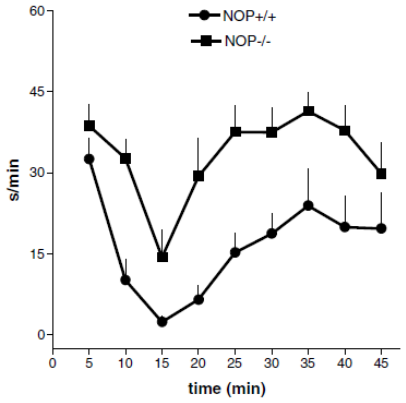
OFF test – endogenous N/OFQ

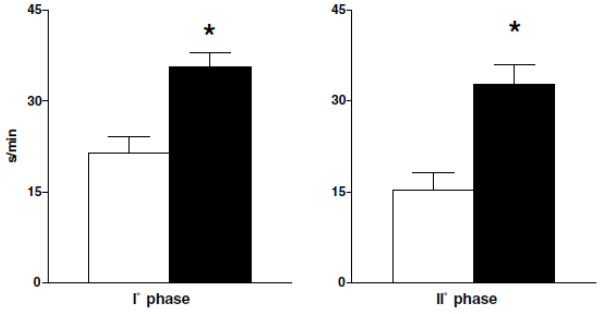




Formalin test – endogenous N/OFQ

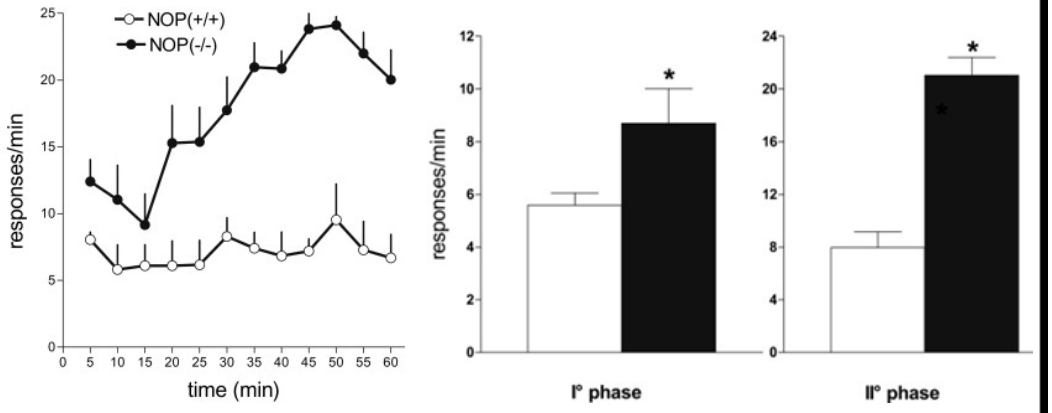
NOP(-/-) mice





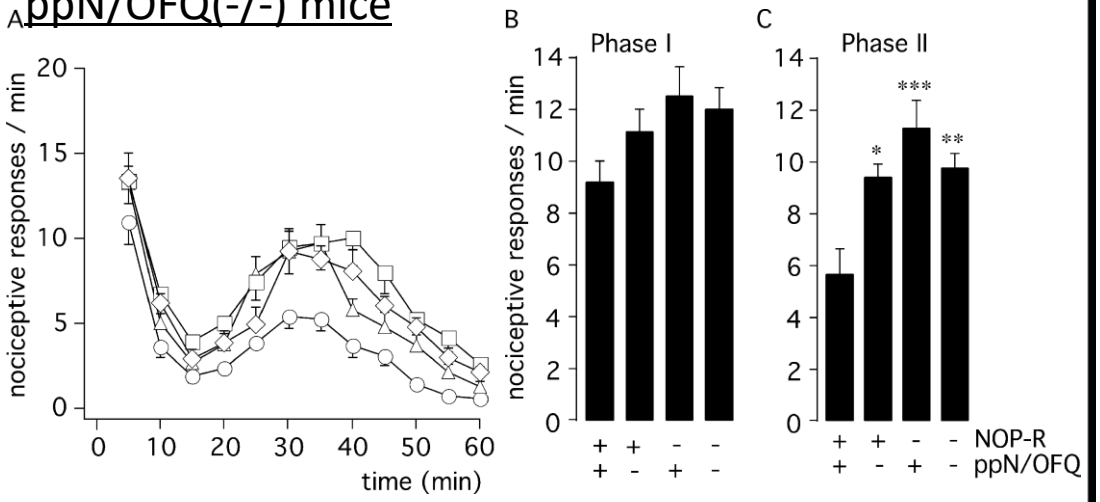
Rizzi et al. 2006

NOP(-/-) rats



Rizzi et al. 2011

ppN/OFQ(-/-) mice



Depner et al. 2003

Cebranopadol: a NOP / mu agonist

PRP Pharmacology Research & Perspectives
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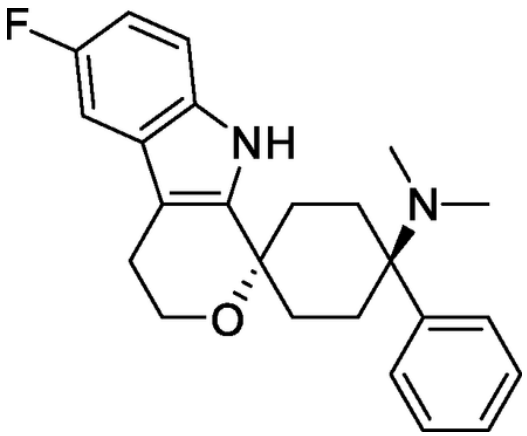
ORIGINAL ARTICLE

Pharmacological characterization of cebranopadol a novel analgesic acting as mixed nociceptin/orphanin FQ and opioid receptor agonist

Anna Rizzi[1,a], Maria Camilla Cerlesi[1,a], Chiara Ruzza[1], Davide Malfacini[1], Federica Ferrari[1], Sara Bianco[2], Tommaso Costa[3], Remo Guerrini[2], Claudio Trapella[2] & Girolamo Calo'[1,]



1521-0103/349/3/535–548$25.00
THE JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS

http://dx.doi.org/10.1124/jpet.114.213694
J Pharmacol Exp Ther 349:535–548, June 2014

al Therapeutics

Cebranopadol: A Novel Potent Analgesic Nociceptin/Orphanin FQ Peptide and Opioid Receptor Agonist[S]

Klaus Linz, Thomas Christoph, Thomas M. Tzschentke, Thomas Koch, Klaus Schiene, Michael Gautrois, Wolfgang Schröder, Babette Y. Kögel, Horst Beier, Werner Englberger, Stefan Schunk, Jean De Vry, Ulrich Jahnel, and Stefanie Frosch

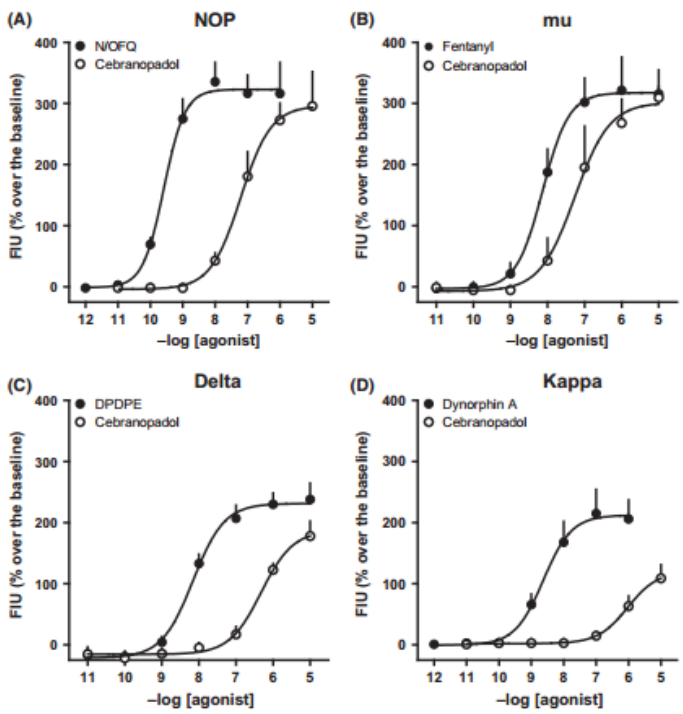
PAIN Practice

ORIGINAL ARTICLE

Antihyperalgesic, Antiallodynic, and Antinociceptive Effects of Cebranopadol, a Novel Potent Nociceptin/Orphanin FQ and Opioid Receptor Agonist, after Peripheral and Central Administration in Rodent Models of Neuropathic Pain

Thomas M. Tzschentke, PhD*; Klaus Linz, PhD†; Stefanie Frosch, PhD†; Thomas Christoph, PhD*
*Pharmacology and Biomarker Development, Grünenthal GmbH; †Preclinical Drug Development, Grünenthal GmbH, Aachen, Germany

Cebranopadol: a NOP / mu agonist



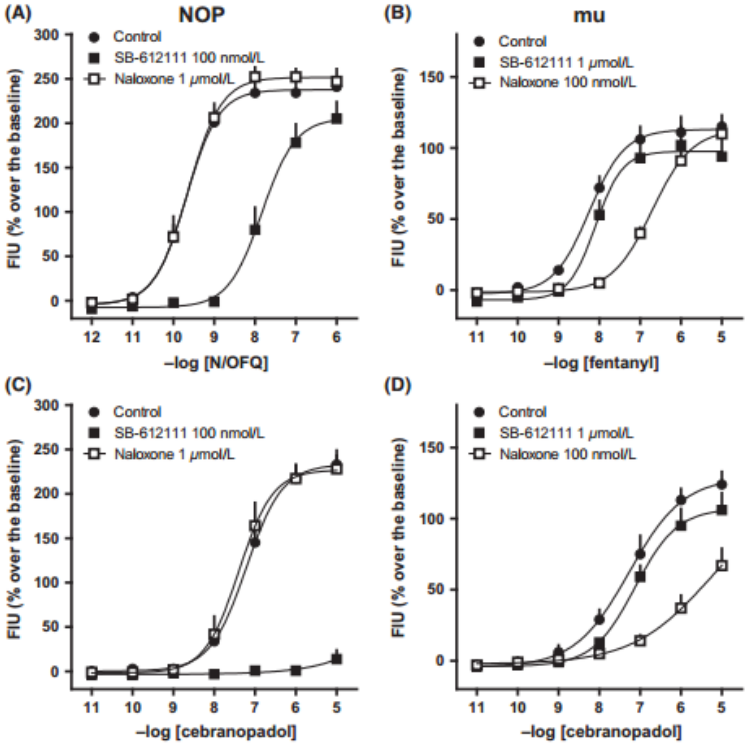
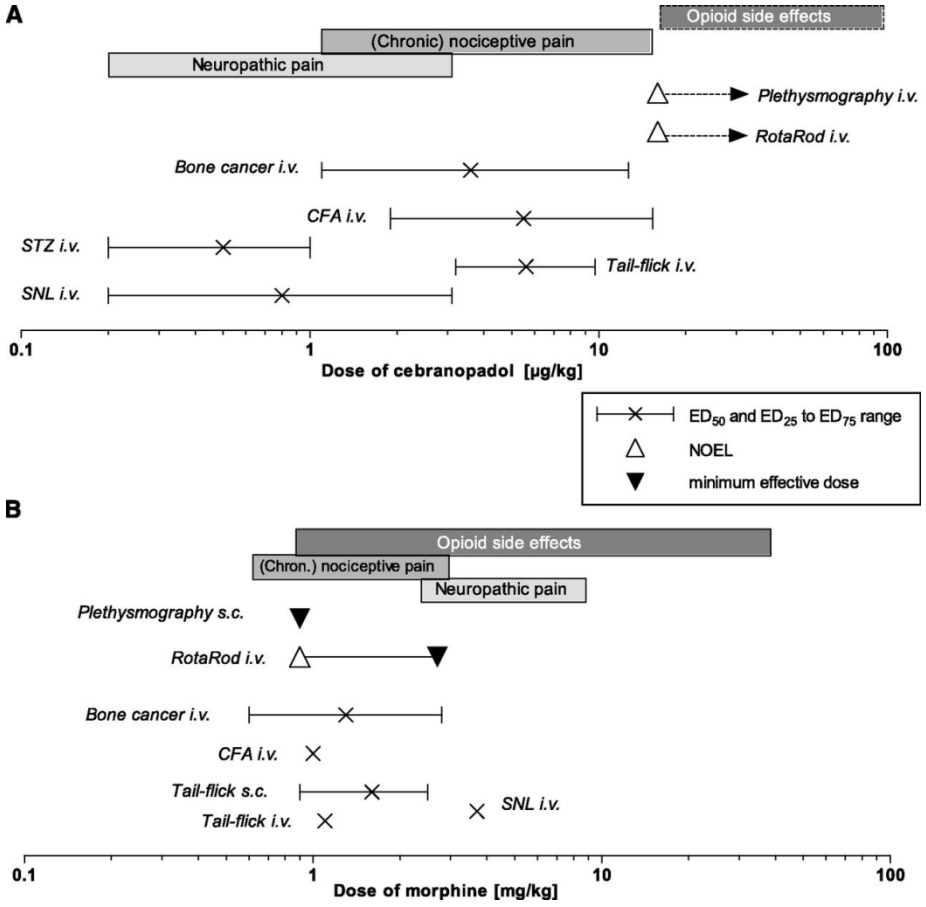


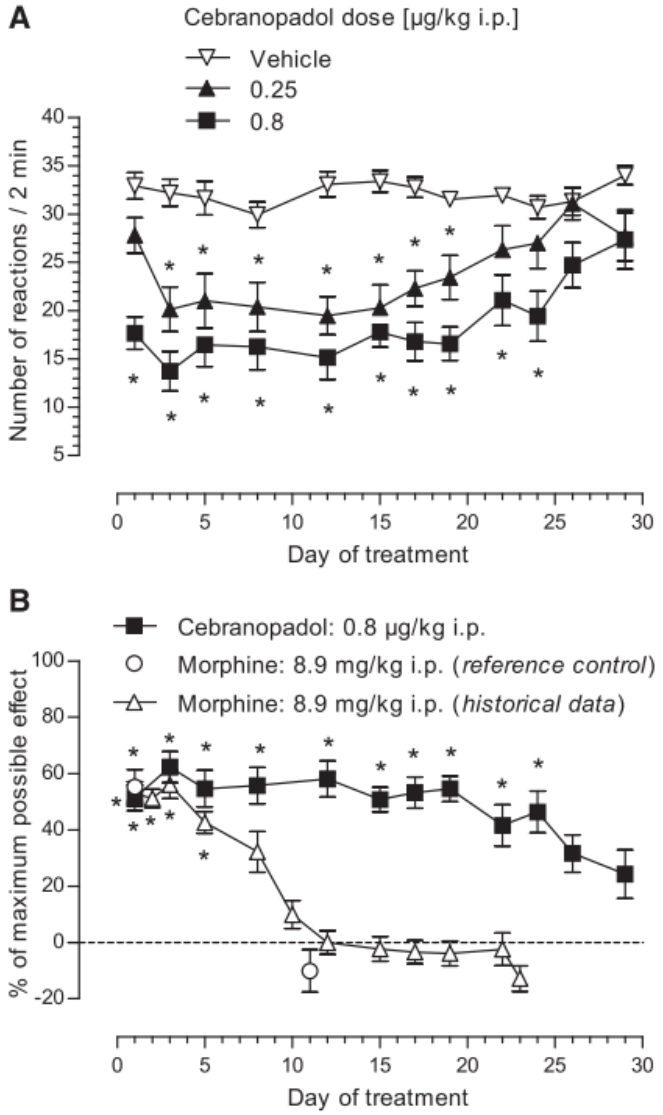
Table 1. Calcium mobilization studies. Potencies and efficacy of N/OFQ, cebranopadol, and standard opioid agonists in CHO cells expressing the human NOP or classical opioid receptors and chimeric proteins.

	NOP		mu		delta		kappa	
	pEC_{50} ($CL_{95\%}$)	α ± SEM	pEC_{50} ($CL_{95\%}$)	α ± SEM	pEC_{50} ($CL_{95\%}$)	α ± SEM	pEC_{50} ($CL_{95\%}$)	α ± SEM
N/OFQ	9.59 (9.49–9.68)	1.00	Inactive		Inactive		Inactive	
Fentanyl	Inactive		8.13 (7.90–8.37)	1.00	Inactive		Inactive	
DPDPE	Inactive		Inactive		8.15 (7.88–8.43)	1.00	Inactive	
Dynorphin A	Inactive		6.67 (6.17–7.17)	0.82 ± 0.10	7.73 (7.46–8.00)	0.99 ± 0.05	8.54 (8.18–8.90)	1.00
Cebranopadol	7.28 (6.74–7.81)	0.89 ± 0.06	7.20 (6.51–7.88)	0.99 ± 0.05	6.31 (5.71–6.90)	0.81 ± 0.06	5.98 (5.69–6.27)	0.55 ± 0.03*

Rizzi et al. 2016

Cebranopadol: a NOP / mu agonist





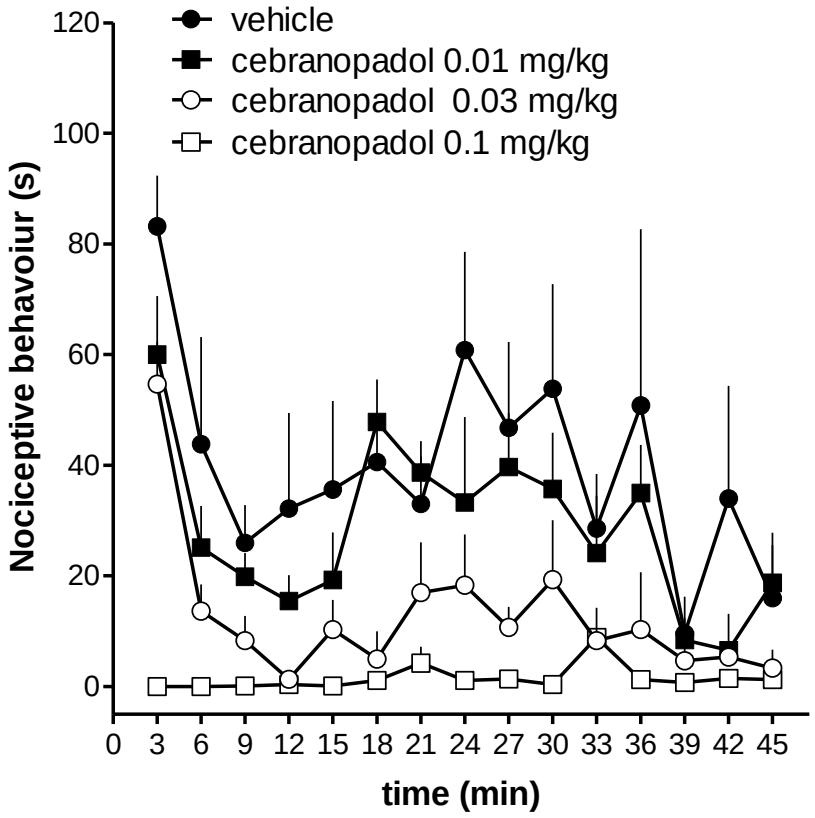
Linz et al. 2014

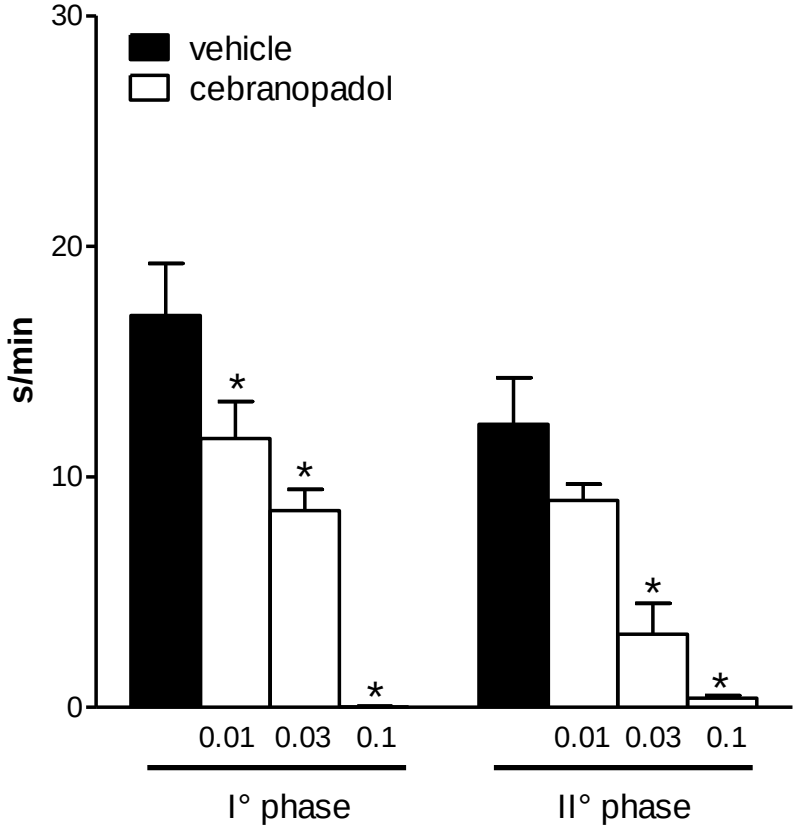
Cebranopadol: a NOP / mu agonist

Table 1 Registered clinical trials with cebranopadol (GRT6005). Total anticipated enrolment: 2976 patients. CORAL + open label extension, Cebranopadol versus morphine prolonged release in patients with chronic moderate to severe pain related to cancer

Indication	Details	Status
Pain: Osteoarthritis	Phase IIa; efficacy, safety, tolerability. Random placebo-controlled. Enrolment 207	Completed
Pain: chronic low back	Phase II; efficacy, safety. Random, placebo, and active (Tapentadol) control. Enrolment 1089	Completed
Pain: osteoarthritis	Phase II; safety, efficacy. Random, placebo, and active (oxycodone) control. Enrolment 619	Completed
Pain: diabetic polyneuropathy	Phase II; efficacy, safety, tolerability. Random placebo-controlled. Enrolment 189	Completed
Pain: bunionectomy	Phase IIa; efficacy, safety, tolerability. Random, placebo, and active (morphine) control. Enrolment 258	Completed
Polyneuropathy	Phase IIa; efficacy, safety, tolerability. Random, placebo, and active (morphine) control. Enrolment 90	Completed
Pain: diabetic neuropathy	Phase II; efficacy, safety and tolerability. Random placebo control. Comparison with Lyrica. Enrolment 350	Recruiting
CORAL+open label extension	Phase III; efficacy, safety, tolerability. Random, placebo, and active (morphine) control. Enrolment 524. Extension is open label. Enrolment 220	Recruiting

OFF test – cebranopadol





ED_{50} 0.02 mg/kg