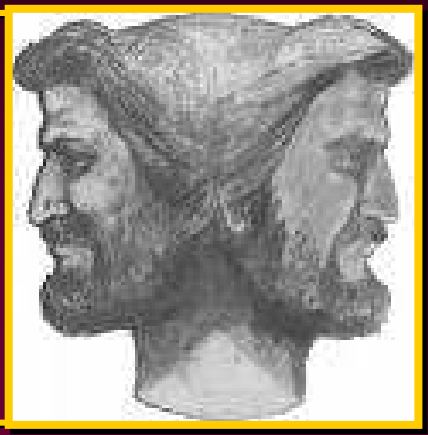
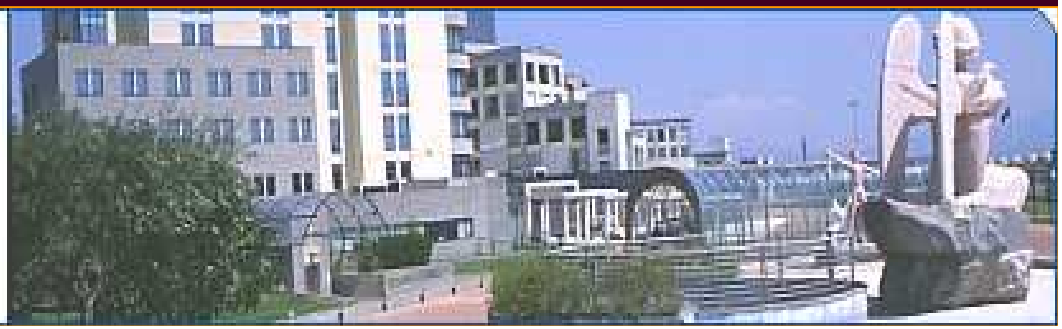
INCONTRI SARDO EUROPEI DI TERAPIA DEL DOLORE E CURE PALLIATIVE
BUDONI 3/4/5 OTTOBRE 2008

L'AMBIVALENTE RUOLO DI OPPIATI ED OPPIOIDI: ANALGESIA ED IPERALGESIA

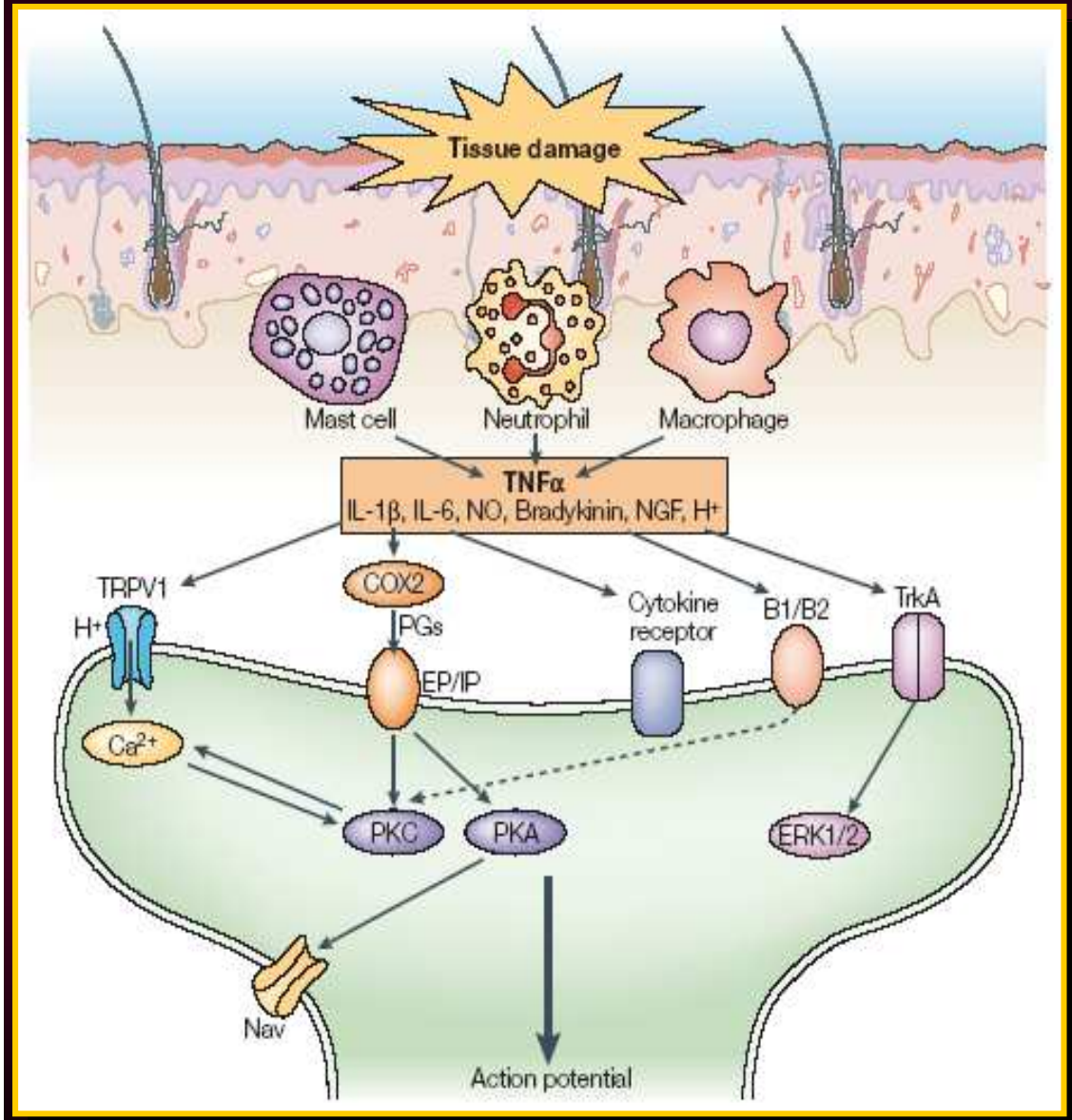


Prof. Edoardo Arcuri
UOC di Rianimazione Terapia Intensiva
Terapia del Dolore e Cure Palliative
Istituto Regina Elena - IFO - Roma

Ifo ISTITUTI FISIOTERAPICI OSPITALIERI



IPERALGESIA "FISIOLOGICA" IMMUNOMEDIATA



DOLORE INFIAMMATORIO: Mast cells – macrofagi attivati e neutrofili stravasati producono mediatori che agiscono su recettori specifici posti su nocicettori o su terminali di fibre nervose afferenti che vengono così attivate.

RECETTORI:
COX2 Ciclossigenasi
B1/B2 Bradichinina
EP/IP Prostanoidi
ERK1/2 Extracell.Sig.Reg.Kin.
Na/v Canali Na Voltaggio Dip.
PGs Prostaglandine
PKA/C Protein Kinasi A/C
TrkA Tyrosine Kinasi A REC
TRPV1 Transient Pot. Rec Chan

Porreca et al.

Can inflammation relieve pain?

Immune cells secreting the opioid peptide β-endorphin undergo selectin-mediated migration to peripheral sites of injury where they promote analgesia (pages 1425–1428).

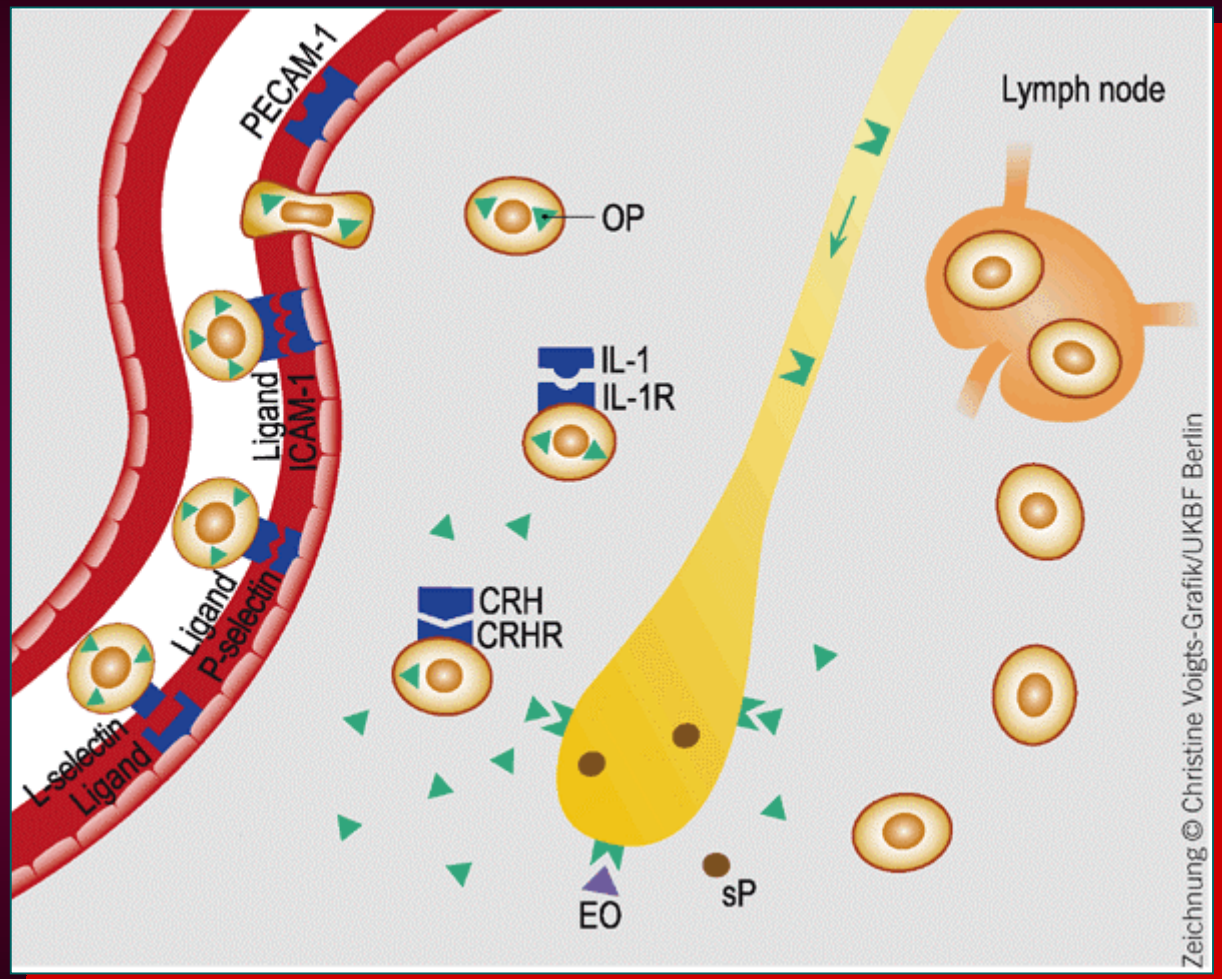
Nat.Med.

Machelska H, Cabot PJ, Mousa SA, Zhang Q, Stein C.
PAIN CONTROL IN INFLAMMATION GOVERNED BY SELECTINS.
Nat Med. 1998 Dec;4(12)1425-8.

…….These findings indicate that the immune system uses mechanisms of cell migration not only to fight pathogens but also to control pain in injured tissue. Thus, pain is exacerbated by measures inhibiting the immigration of opioid-producing cells or, conversely, analgesia might be conveyed by adhesive interactions that recruit those cells to injured tissue.

…… SOLO SE INFIAMMAZIONE

La migrazione di leucociti capaci di rilasciare oppiati è regolata da molecole di adesione e da selectine L e P



Stein C. et al. Nat.Med. 2003

LESIONE

↓

CRF e IL1β

↓

RELEASE DI OPPIOIDI

↓

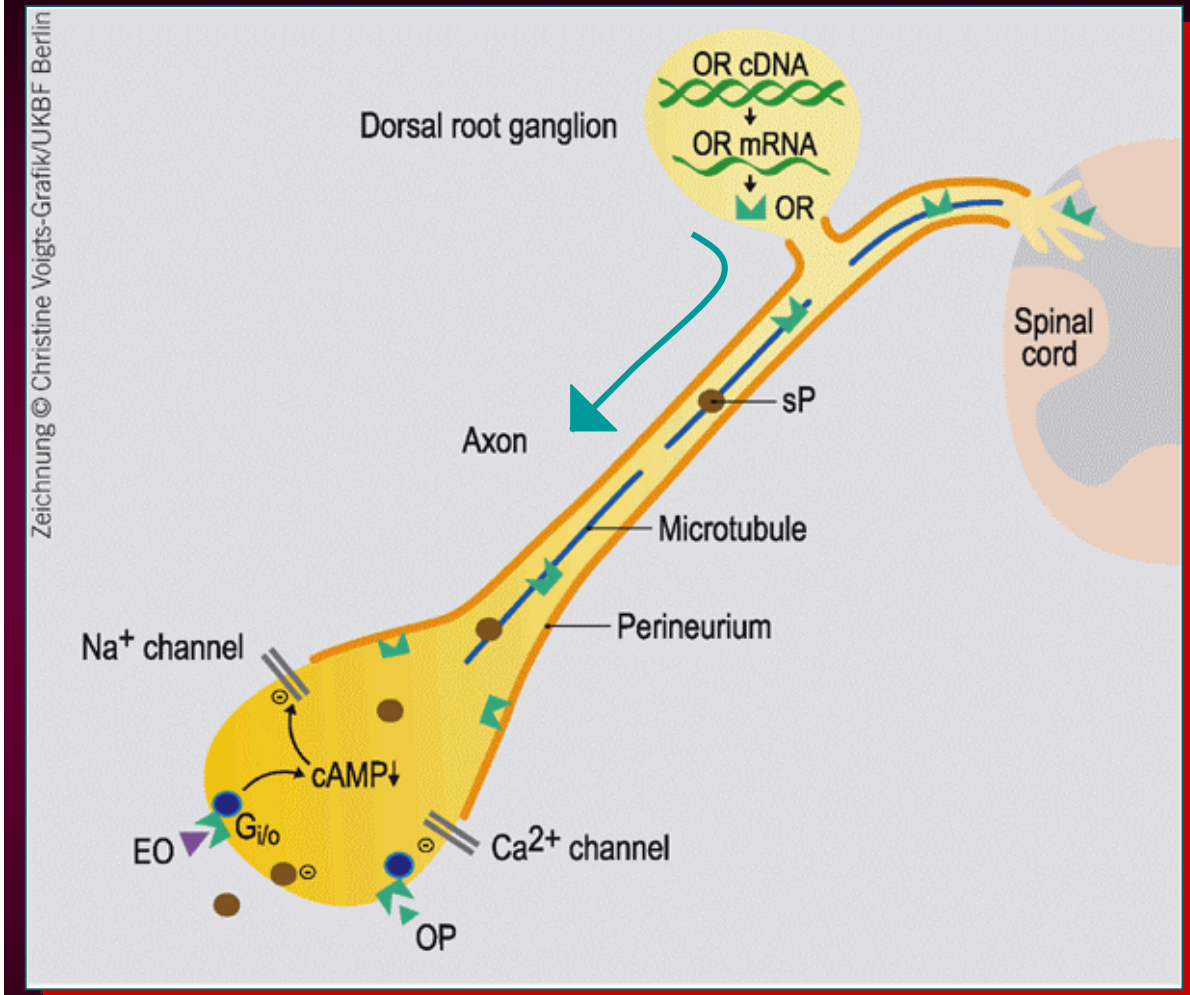
OVERESPRESSIONE OR

↓

ANTAGONISMO DI IPERALGESIA LOCALE

ANALGESIA ENDOGENA PERIFERICA

STIMOLAZIONE / LESIONE DI TERMINALI AFFERENTI



AUMENTATA SINTESI di OR nei DRG

MIGRAZIONE ASSONALE

INCLUSIONE IN MEMBRANA CELLULARE COME RECETTORI FUNZIONALI

King M, Su W, Chang A, Zuckerman A, Pasternak GW.
Transport of opioids from the brain to the periphery by P-glycoprotein: peripheral actions of central drugs.
Nat Neurosci. 2001 Mar;4(3):268-74

OPIODS AS CYTOKINES

By an autocrine – paracrine circuit, the immune – derived opioids exert two opposite effects

STIMULATION
of the primitive inflammatory response

INHIBITION
of immune response: negative feedback control

OVERSTIMULATION

Tumor-Rubror-DOLOR-Calor-Functio lesa

CHRONIC INFLAMMATION

ANALGESIA/IPERALGESIA OPPIOIDO-IMMUNOMEDIATA

L'insufficienza del sistema di analgesia endogena periferica attiva un processo di sensibilizzazione centrale che si traduce in varie forme di Iperalgesia:

- ***da somministrazione acuta***
- ***da somministrazione cronica***
- ***da somministrazione incongrua***
- ***da interazione oppioidi/tumore***
- ***iperalgesia nocebo***

PREEMPTIVE HYPERALGESIA, NOT ANALGESIA?

DESPITE its logical appeal and strong support in animal experiments, there is relatively little evidence in humans after surgery for the phenomenon of "preemptive analgesia." Thus, providing intense analgesia from large doses of systemic or epidural–spinal medications before and during surgery (even extending into the acute postoperative period) appears to exert no or only modest effects on subsequent pain experience or analgesic requirements. The study by Célèrier et al. may give us a clue for one reason for this failure of a strong clinical effect by preemptive analgesic therapy. ……The more the fentanyl administered acutely, the greater this hyperalgesic effect. If such an effect occurs in humans, then part of the lack of preemptive analgesia, at least from systemic opioids, could reflect development of sustained hyperalgesia from previous opioid exposure.

Eisenach JC. Anesthesiology, 92 (2) Feb 2000 (Editorial)

Celerier E. et al. Long-lasting Hyperalgesia Induced by Fentanyl in Rats. Preventive Effect of Ketamine. Anesthesiology, 2000

DOLORE "DRIVING FORCE" DELL'ANALGESIA.

NO PAIN NO GAIN

"Short-term infusion of the μ-opioid agonist remifentanil in humans causes hyperalgesia during withdrawal"

(W. Koppert et al. Pain Nov.2003)

"Naloxone provokes similar pain facilitation as observed after short-term infusion of remifentanil in humans"

(M.Schmelz Pain Nov.2003)

IPERALGESIA DEL MANTENUTO

"Hyperalgesic responses in methadone maintenance patients"

(Doverty M. et al Pain. 2001;90)

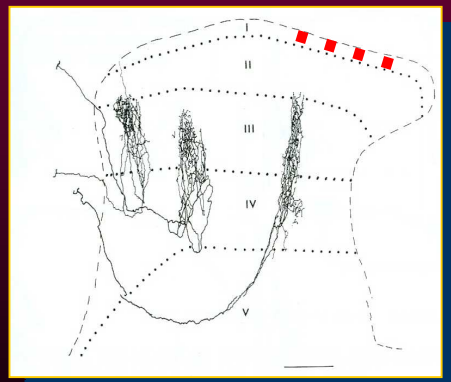
"Methadone maintenance patients are cross-tolerant to the antinociceptive effects of morphine"

Doverty M. et al Pain. 2001; 93)

IL SUPPLIZIO DI TANTALO

MECCANISMI E VIE DELLA IPERALGESIA OPPIOIDO-INDOTTA

- *Imbalance controllo oppioideo pre-post sinaptico*
- *Overespressione di recettori NMDA*
- *Upregulation del recettore per la dinorfina*
- *Upregulation del recettore per la colecistichinina (CCK)*
- *Apoptosi delle cellule della lamina I delle corna dorsali*
- *Imbalance del sistema sopraspinale di inibizione/facilitazione del dolore (on/off cells)*



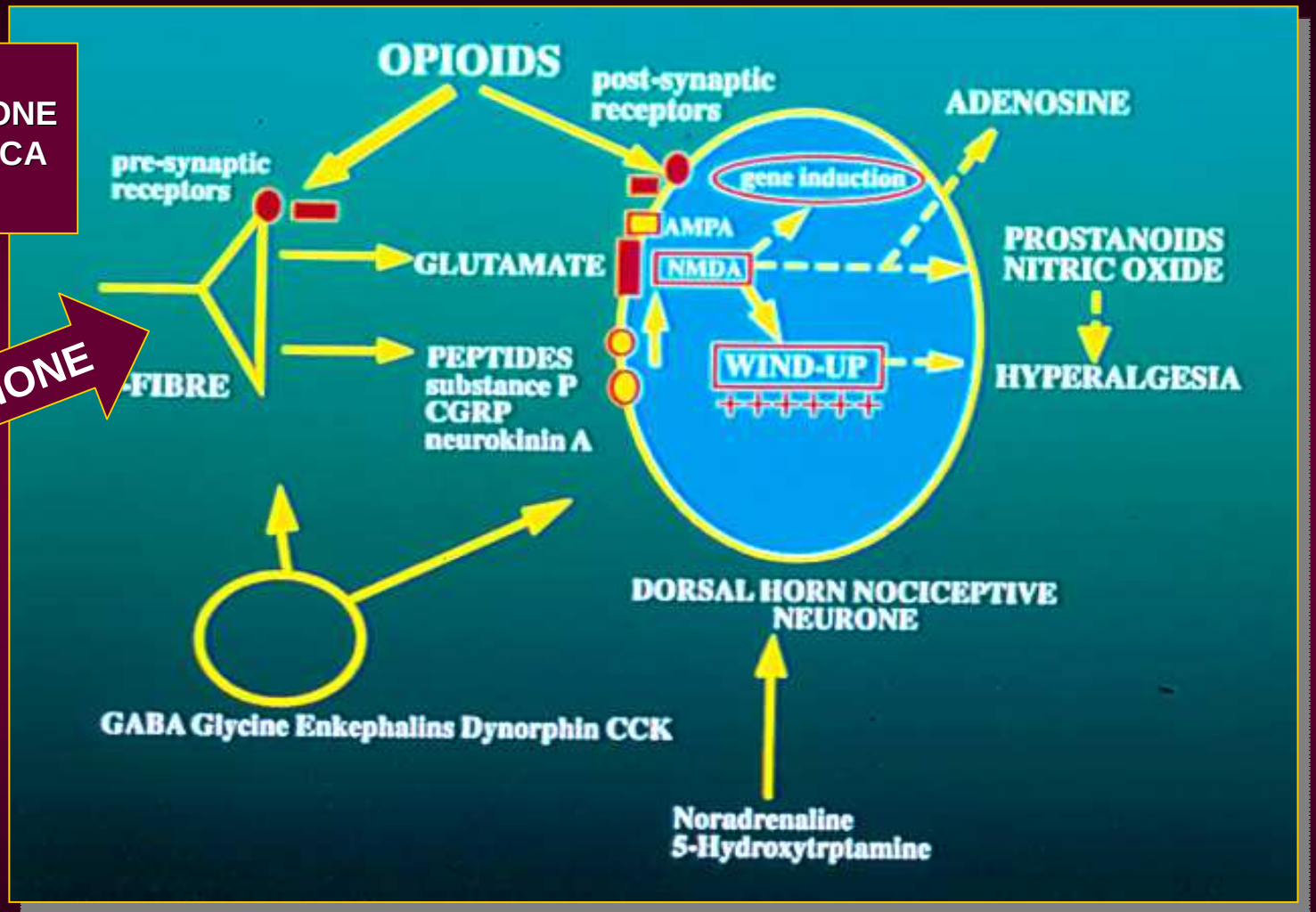
Vanderah TW, Ossipov MH, Lai J, Malan TP Jr, Porreca F.

Mechanisms of opioid-induced pain and antinociceptive tolerance: descending facilitation and spinal dynorphin.

Pain. 2001 May;92(1-2):5-9.

Overespressione di RMNDA nel SNC

PER SOMMINISTRAZIONE ACUTA O CRONICA DI OPPIOIDI

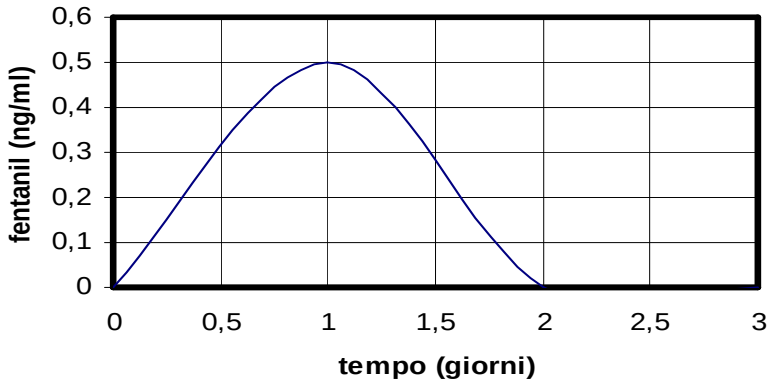


Stanfa LC, Dickenson AH. THE ROLE OF NON-N-METHYL-D-ASPARTATE IONOTROPIC GLUTAMATE RECEPTORS IN THE SPINAL TRANSMISSION OF NOCICEPTION IN NORMAL ANIMALS AND ANIMALS WITH CARRAGEENAN INFLAMMATION. Neuroscience. 1999;93(4):1391-8.

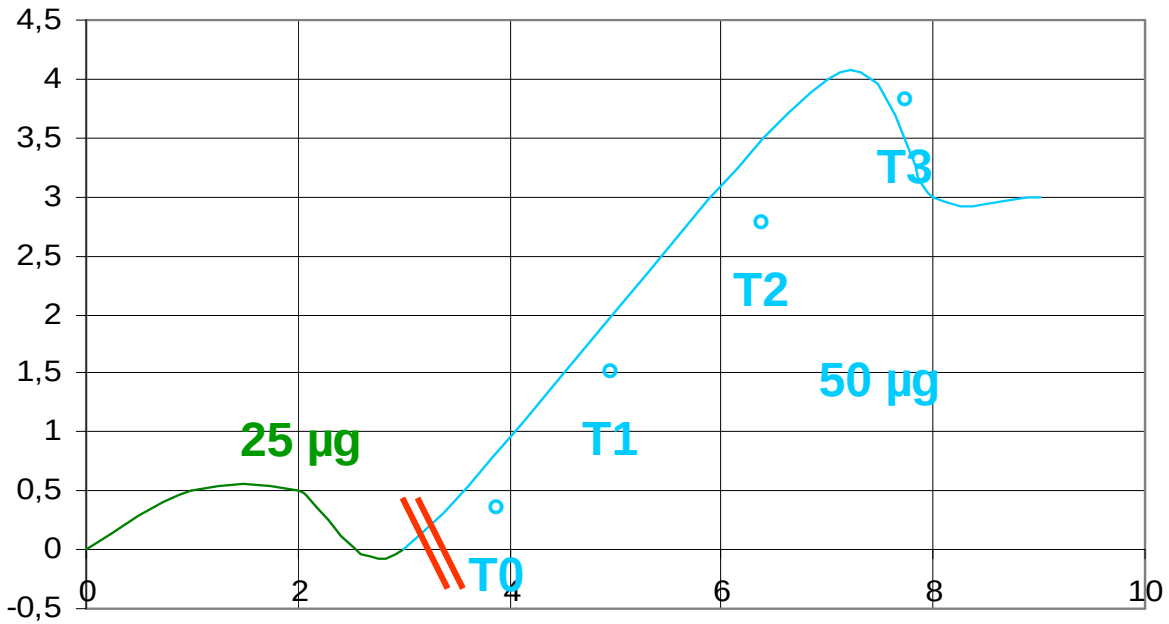
Concentrazione del Fentanyl (25 µg) in un paziente alla prima somministrazione (HPLC)

T0	VAS 8
T1	VAS 2
T2	VAS 2
T3	VAS 4

T.T. ♂ 58 a.



N.G. ♂ 78 a.



25 → 50 µg

T0	VAS 7
T1- T2	VAS 1
	4 gg
T0	VAS 7
T1	VAS 2
T2 – T3	VAS 0

TIMING → IPERALGESIA … ?

NEI TUMORI TOLLERANZA-IPERALGESIA-DOLORE NEUROPATICO E SCARSA RESPONSIVITÀ AGLI OPPIOIDI SONO "DIVERSI"?

- **Sjogren P. et al. Disappearance of morphine-induced hyperalgesia after discontinuing or substituting morphine with other opioid agonists.**
  Pain1994;59:313-316.

- **Faisinger RL, Bruera E. Is this opioid analgesic tolerance?**
  ***J Pain Symptom Manage*. 1995 Oct;10(7):573-7.**

- **Arcuri E. Can tumors act as opioid traps, mimicking opioid tolerance?**
  ***J Pain Symptom Manage* 1998 Aug;16(2):78-9.**

Andersen G, Sjøgren P, Hansen SH, Jensen NH, Christrup L.

PHARMACOLOGICAL CONSEQUENCES OF LONG-TERM MORPHINE TREATMENT IN PATIENTS WITH CANCERAND CHRONIC NON-MALIGNANT PAIN.

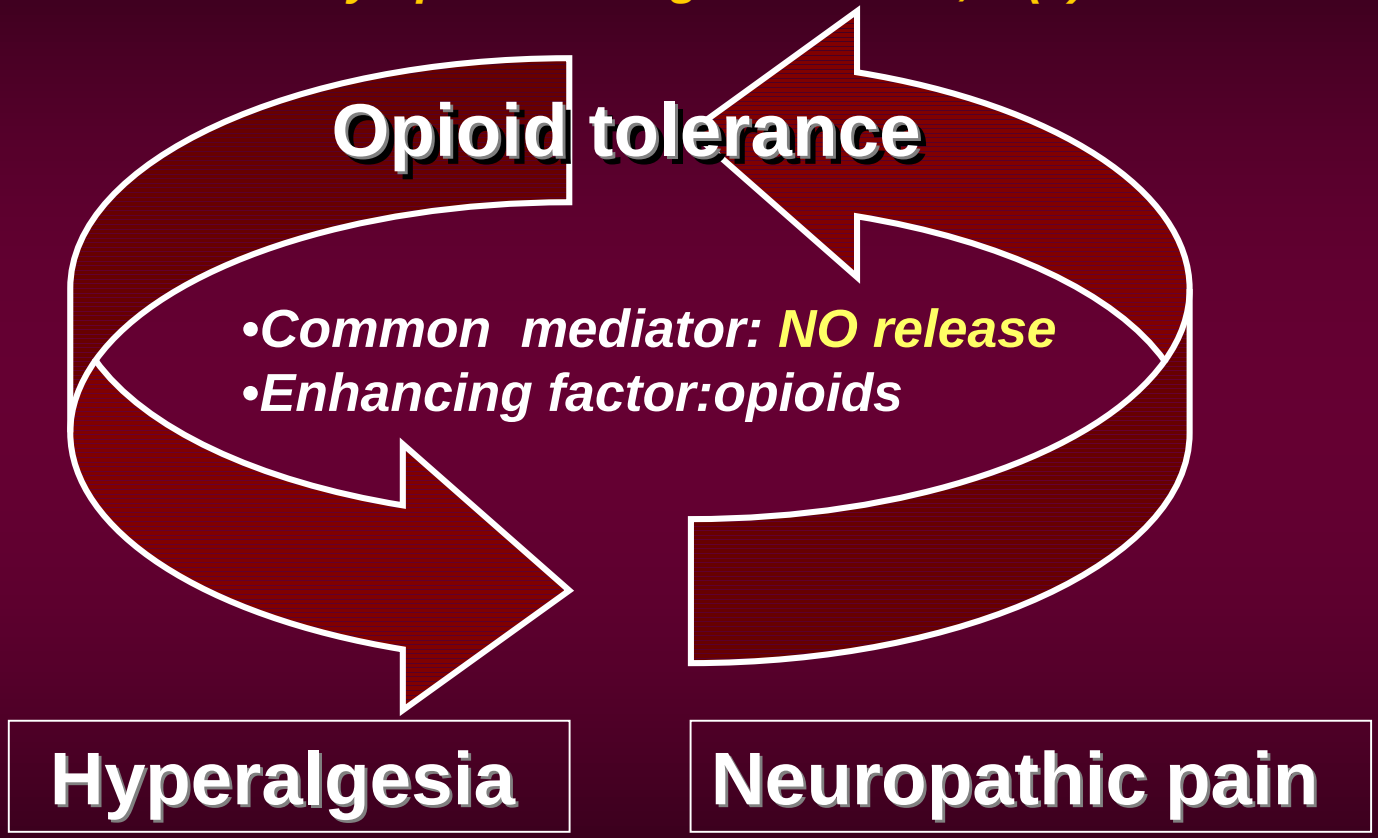
Eur J Pain. 2004 Jun;8(3):263-71.

BACKGROUND: In patients with pain of malignant origin morphine may be administered in high and often increasing doses during extended periods of time. In patients with chronic pain of non-malignant origin morphine may be an important remedy, and in these cases the goal is to keep the morphine dose stable. The pharmacokinetic as well as the pharmacodynamic consequences of long-term morphine treatment with special reference to the two most important metabolites of morphine morphine-6-glucuronide (M-6-G) and morphine-3-glucuronide (M-3-G) remain to be settled.

CONCLUSION: In the cancer patient group neither dose nor treatment period seems to influence morphine glucuronidation. Likewise in the non-cancer patient group receiving stable doses of morphine duration of treatment does not seem to influence morphine glucuronidation. Dryness of the mouth was positively correlated to high plasma concentrations of morphine and M-6-G.

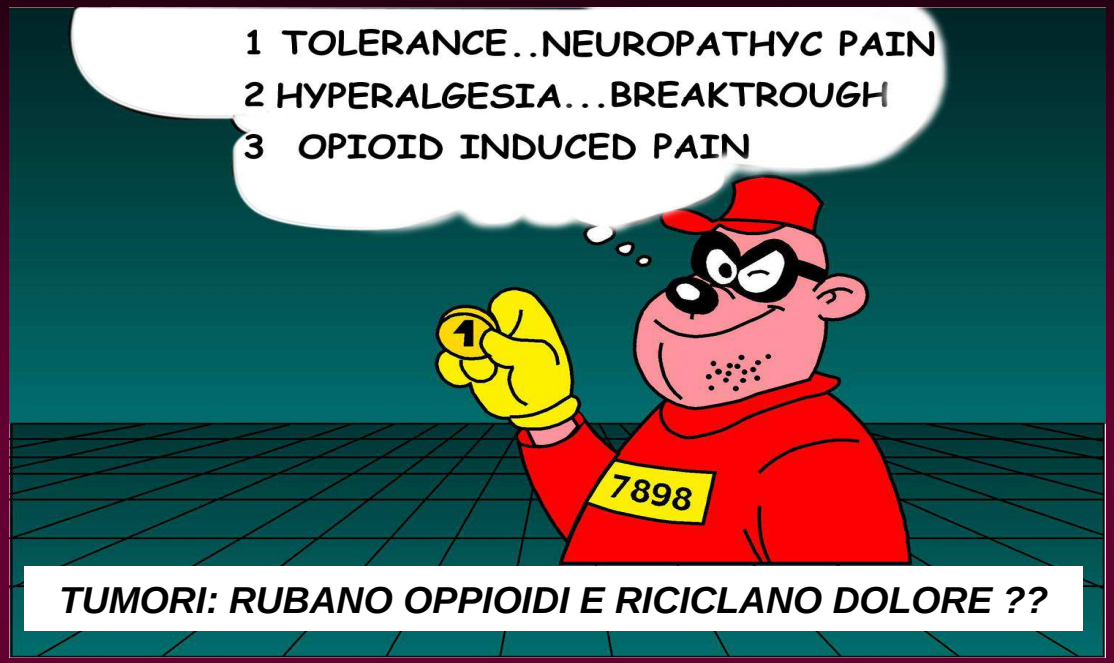
A DANGEROUS FEEDBACK LOOP…

Mercadante S. Portenoy R. "Opioid poorly-responsive cancer pain. Part 2: basic mechanisms that could shift dose response for analgesia". J Pain Symptom Manage. 2001 Mar;21(3):255-64.



Mercadante S, Ferrera P, Villari P, Arcuri E.. "Hyperalgesia: An Emerging Iatrogenic Syndrome". J Pain Symptom Manage 2003 Aug;26(2):1-7

EVIDENZE SPERIMENTALI DEL TRAPPING TUMORALE DI MORFINA (1) E DEL SUO EFFETTO FUNZIONALE (NO RELEASE) (2).



2."Mu3 opiate receptor expression in lung and lung carcinoma: ligand binding and coupling to nitric oxide release."
Fimiani C, Arcuri E, Santoni A, Rialas CM, Bilfinger TV, Peter D, Salzet B, Stefano GB.Cancer Lett 1999 Nov 1;146(1):45-51

1. "Preliminary in vivo evidence on intratumoral morphin uptake. Possibile clinical implication in cancer pain and opioid responsiveness"
E. Arcuri et al;J. Pain Symptom Manage. July 2002

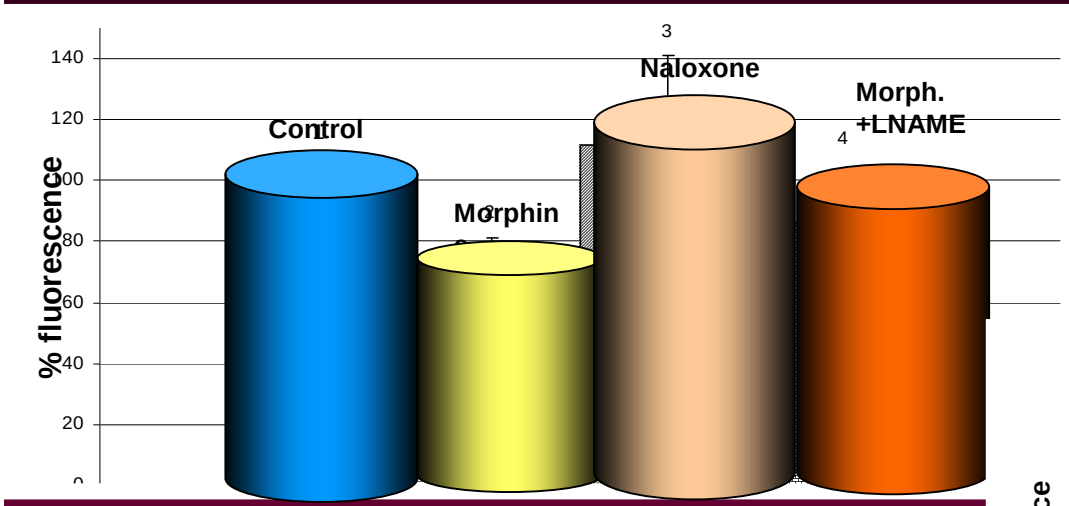
UN FUTURO CAMPO DI RICERCA

Oppioidi diversi interagiscono con diversi tumori provocando Dolore cosiddetto neuropatico ed iperalgesia di differente grado? Esistono "tollerogenicità" diverse sotto questo profilo??

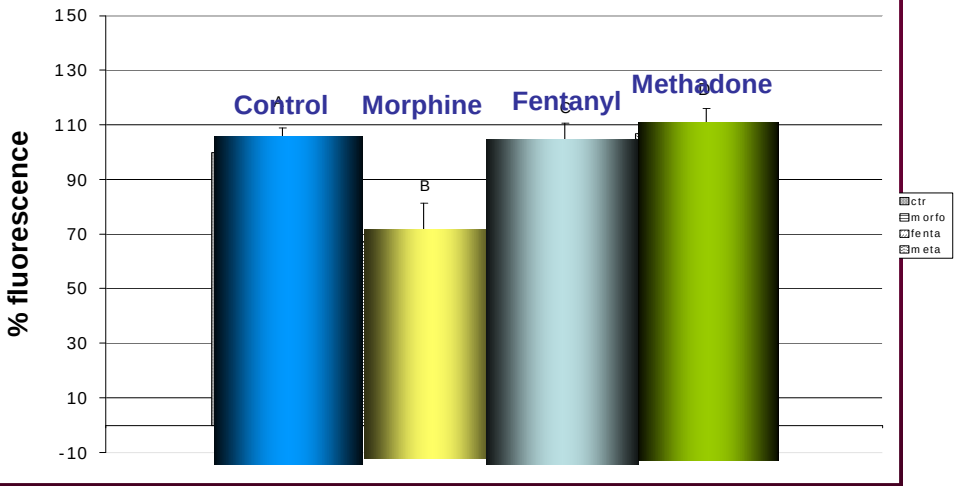
Il loro impiego nel dolore cronico non maligno sta dimostrando che gli oppioidi non sono "uguali": tolleranza e iperalgesia

appaiono attualmente mediate e proporzionali ai variabili effetti immunitari degli oppioidi

Marked NO release by morphine on glioma cell



Effect undetectable with Fentanil or Methadone



D. Mastronicola, E. Arcuri, S Mercadante, M. Arese, A Bacchi, P. Cardelli, G. Citro and P. Sarti
"Morphine but not fentanyl and methadone affects mitochondrial membrane potential by inducing NO release in glioma cells".
***Cellular and Molecular Life Sciences* 61 (2004)**

Pain 118 (2005) 8–9

ww

Editorial

Opioids: From analgesia to anti-hyperalgesia?

Different profiles of buprenorphine-induced analgesia and antihyperalgesia in a human pain model

Wolfgang Koppert[a,*], Harald Ihmsen[a], Nicole Körber[a], Andreas Wehrfritz[a], Reinhard Sittl[a], Martin Schmelz[b], Jürgen Schüttler[a]

[a]*Department of Anaesthesiology, University Hospital Erlangen, Krankenhausstrasse 12, D-91054 Erlangen, Germany*
[b]*Department of Anaesthesiology Mannheim, University of Heidelberg, Theodor-Kutzer Ufer 1-3, D-61087 Mannheim, Germany*

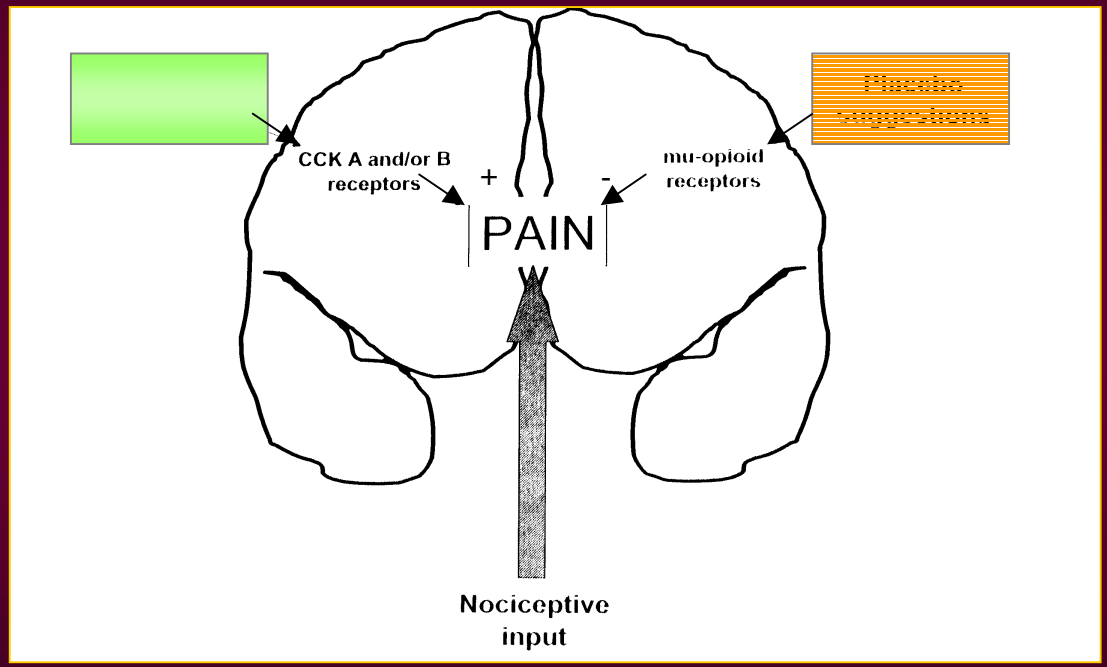
Received 7 February 2005; received in revised form 17 May 2005; accepted 20 June 2005

Abstract

Different mechanisms were proposed for opioid-induced analgesia and antihyperalgesia, which might result in different pharmacodynamics. To address this issue, the time course of analgesic and antihyperalgesic effects of intravenous (i.v.) and sublingual (s.l.) buprenorphine was assessed in an experimental human pain model. Fifteen volunteers were enrolled in this randomized, double-blind, and placebo controlled cross-over study. The magnitude of pain and the area of secondary hyperalgesia following transcutaneous stimulation were repetitively assessed before and up to 150 min after administration of (1) 0.15 mg buprenorphine i.v. and placebo pill s.l., (2) 0.2 mg buprenorphine s.l. and saline 0.9% i.v. or (3) saline 0.9% i.v. and placebo pill s.l. as a control. The sessions were separated by 2 week wash-out periods. For both applications of buprenorphine the antihyperalgesic effects were more pronounced as compared to the analgesic effects (66±9 vs. 26±5% and 43±10 vs. 10±6%, for i.v. and s.l. application, respectively). This contrasts the pattern for the intravenous administration of pure μ-receptor agonists in the same model in which the antihyperalgesic effects are weaker. The apparent bioavailability of buprenorphine s.l. as compared to buprenorphine i.v. was 58% with a 15.8 min later onset of antinociceptive effects. The half-life of buprenorphine-induced analgesic and antihyperalgesic effects were 171 and 288 min, respectively. In contrast to pure μ-receptor agonists, buprenorphine exerts a lasting antihyperalgesic effect in our model. It will be of major clinical interest whether this difference will translate into improved treatment of pain states dominated by central sensitization.

D.G. Finnis e F. Benedetti
PLACEBO ANALGESIA, NOCEBO HYPERALGESIA
Pain Clinical Updates Vol XV, Issue 1.March 2007

Whereas placebo effects are mediated at least in part by endogenous opiopids, nocebo effects have been found to be mediated predominantly by cholecystokinin (CCK).



The nocebo effect clearly demonstrates the potentially harmful impact of an adverse patient-clinician interaction, whereby negative words and attitudes of the clinician, by altering the context, may induce negative expectations in the patient and subsequent increases in pain.

Attuale orientamento preventivo/terapeutico I
Associazione di routine di farmaci multitarget recettoriali (OPPIOIDI/FANS/CORTISONICI)

Nonsteroidal anti-inflammatory drugs, alone or combined with opioids, for cancer pain: a systematic review.

McNicol E, Strassels S, Goudas L, Lau J, Carr D. *JClinOncol.2004May15;22(10):1975-92*

PURPOSE: To assess the safety and efficacy of nonsteroidal anti-inflammatory drugs (NSAIDs), alone or combined with opioids, for the treatment of cancer pain. PATIENTS AND METHODS: Forty-two trials involving 3,084 patients met inclusion criteria: eight compared NSAID with placebo; 13 compared one NSAID with another; 23 compared NSAID with opioid, NSAID or opioid versus NSAID plus opioid combinations, or NSAID plus opioid combinations versus NSAID plus opioid combinations; and nine studies assessed the effect of increasing NSAID dose. RESULTS: Sixteen studies lasted 1 week or longer and 11 evaluated a single dose. Seven of eight trials demonstrated superior efficacy of single doses of NSAID compared with placebo. Only four of 13 studies reported increased efficacy of one NSAID compared with another; four other studies found that one NSAID had fewer side effects than one or more others. Thirteen of 14 studies found no difference, or minimal clinical difference, when comparing an NSAID plus opioid combination versus either drug alone. Comparisons between various NSAID plus opioid combinations were inconclusive. Four studies demonstrated increased efficacy with increased NSAID dose, without dose-dependent increases in side effects. **CONCLUSION: Heterogeneity of study methods and outcomes precluded meta-analyses. Short duration of studies undermines generalization of findings on efficacy and safety. On the basis of limited data, NSAIDs appear to be more effective than placebo for cancer pain; clear evidence to support superior safety or efficacy of one NSAID compared with another is lacking; and trials of combinations of an NSAID with an opioid have disclosed either no significant difference, or at most a slight but statistically significant advantage, compared with either single entity.**

(Speed of escalation? Tolerance/Hyperalgesia? Total opioid doses?)

Attuale orientamento preventivo/terapeutico II

Identificazione precoce delle situazioni di tolleranza rapida /iperalgesia

- **Prevenzione specifica (farmaci antiNMDA)**
- **Switch spinale anche temporaneo ***
- **Switch o semiswitch oppioideo: associazione ad orario per 24 h a bassi dosaggi di un oppioide dello stesso step diverso da quello in atto (*evidenza non provata*)**

•Arcuri E et al. Opioid nonresponsivness in cancer pain can be reversible. A serendipitous conclusion of retrospective study. JPSM 2000.

Mercadante S. and Arcuri E.
HYPERALGESIA AND OPIOID SWITCHING
Am J Hosp Palliat Care. 2005 Jul-Aug;22(4):291-4.

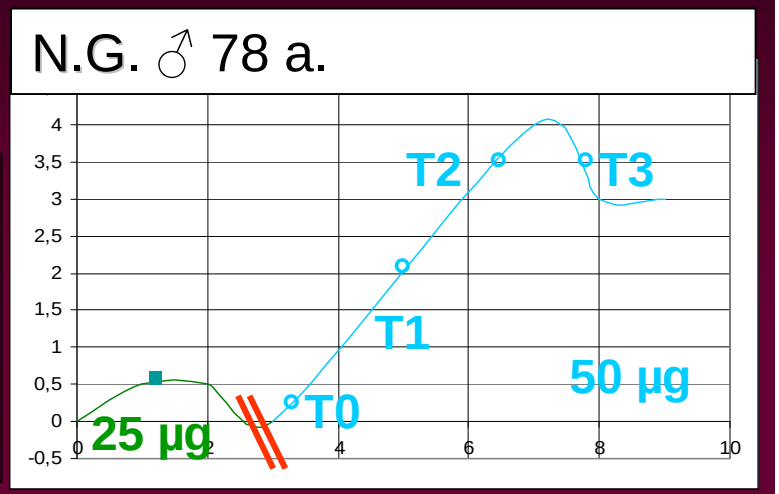
Opioids, intended to abolish pain, can unexpectedly produce hyperalgesia, particularly during rapid opioid escalation. Opioid switching could be a therapeutic option in a condition of opioid-induced tolerance or hyperalgesia, but conversion ratios between opioids are difficult to apply in this context and require strict surveillance and expertise. This situation is challenging, because the rapid escalation of opioid doses, possibly due to the development of opioid-induced tolerance, can cause hyperalgesia. To avoid this adverse effect, clinicians need to refine their assessment of pain treatment and consider opioid switching. The authors present a case report in which switching from fentanyl to methadone was effective in a patient who developed hyperalgesia as a consequence of a rapid opioid escalation. Regardless of the expected clinical improvement of opioid switching using lower doses of the second opioid, the final dose of the second opioid was exaggeratedly low, probably as a consequence of the disappearance of hyperalgesia induced by the first opioid. The results of this case and others like it may help practitioners develop a meaningful approach during opioid escalation, possibly anticipating the need for opioid switching or other alternative measures for patients with uncontrolled cancer pain.

....opioid semiswitching to prevent escalation/tolerance

Attuale orientamento preventivo/ terapeutico III

Evitare analgesia up and down (occupazione costante del recettore)

1) Monitoraggio clinico continuo per aggiustamento dosi e timing.
(tolleranza di intervallo)



2) Opioid semiswitching contemporaneo

3) Switch spinale definitivo