De l'analgésie à l'anti-hyperalgésie

De nouveaux concepts pour de nouvelles thérapies

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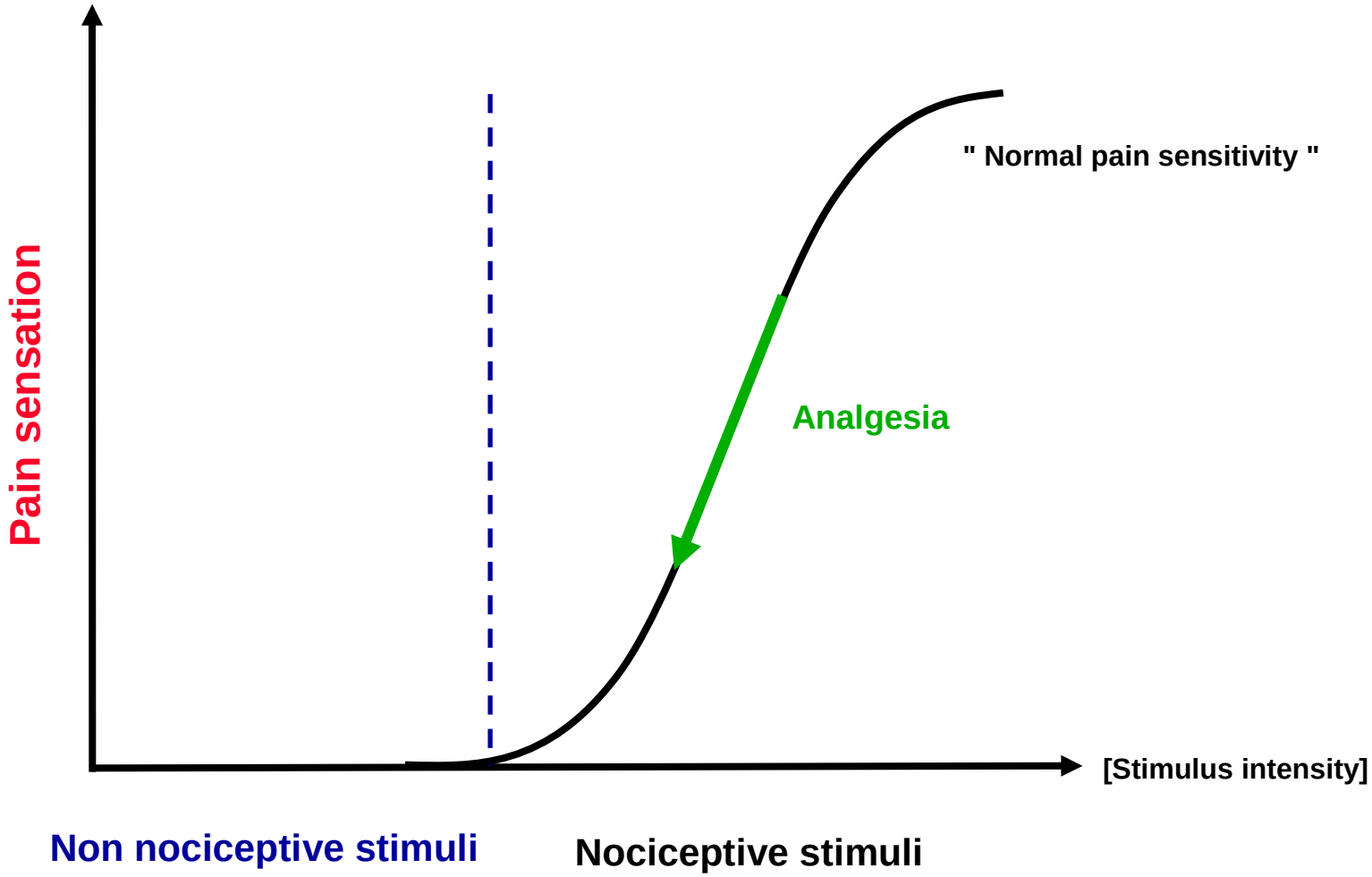

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Epidémiologie et coût des douleurs chroniques

- **10 à 50% des patients opérés ont des douleurs persistantes**
- **61% des patients opérés ont des douleurs anormales > 1 an après une thoracotomie**
- **Un européen sur 5 (19%) souffre de douleur chronique**

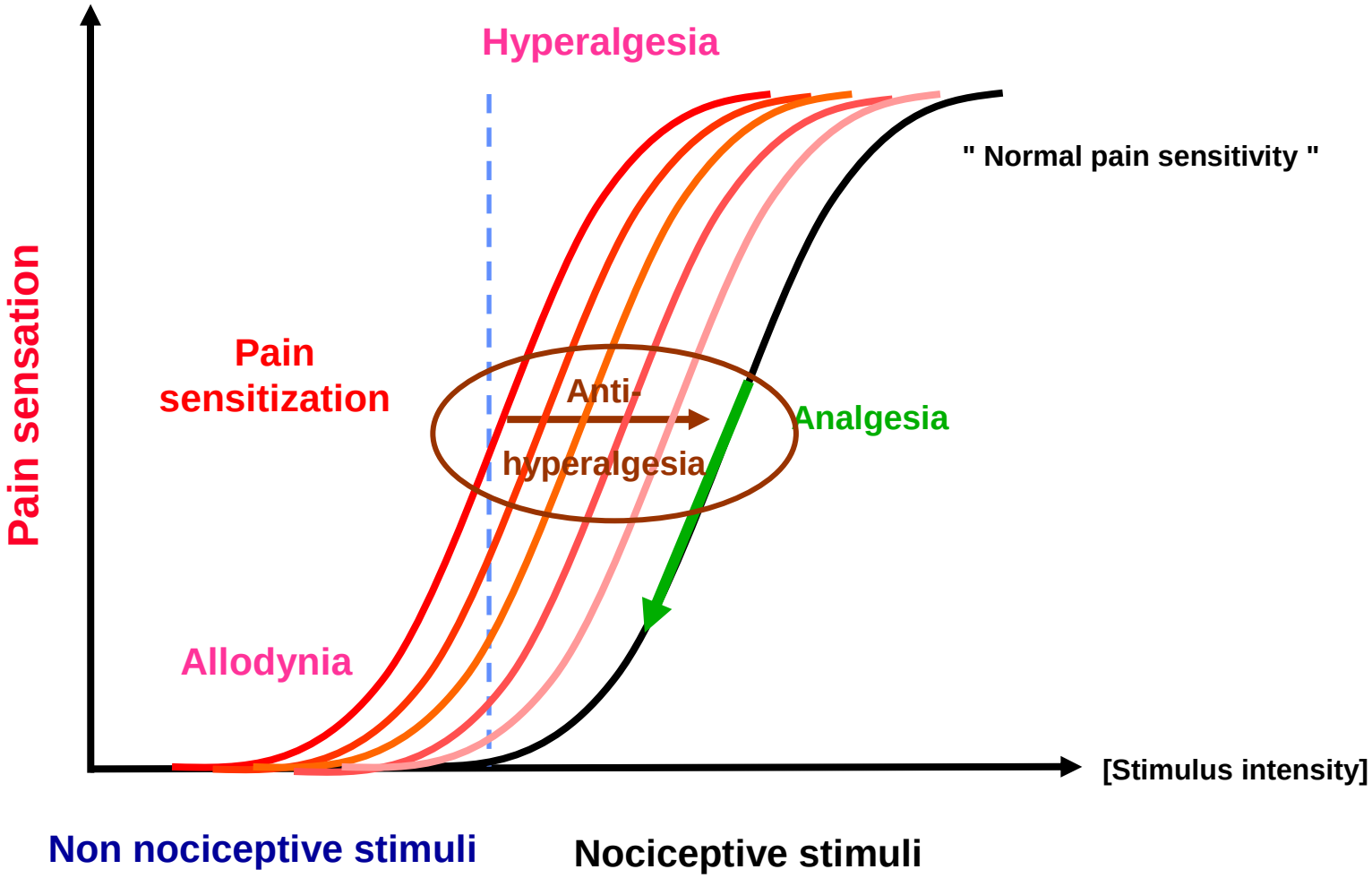
  - 21% des européens atteints de douleur chronique sont totalement incapables de travailler en raison de leur douleur

  - 38% des personnes souffrant de douleur chronique indiquent que la douleur n'est pas gérée de manière adéquate

- **Coût des douleurs chroniques:**

  - 90 milliards de dollars/an aux USA (88 millions d'américains)
  - 300 milliards d'euros en Europe (1.5 à 3% du PIB)

> au coût de l'ensemble des syndromes neurologiques



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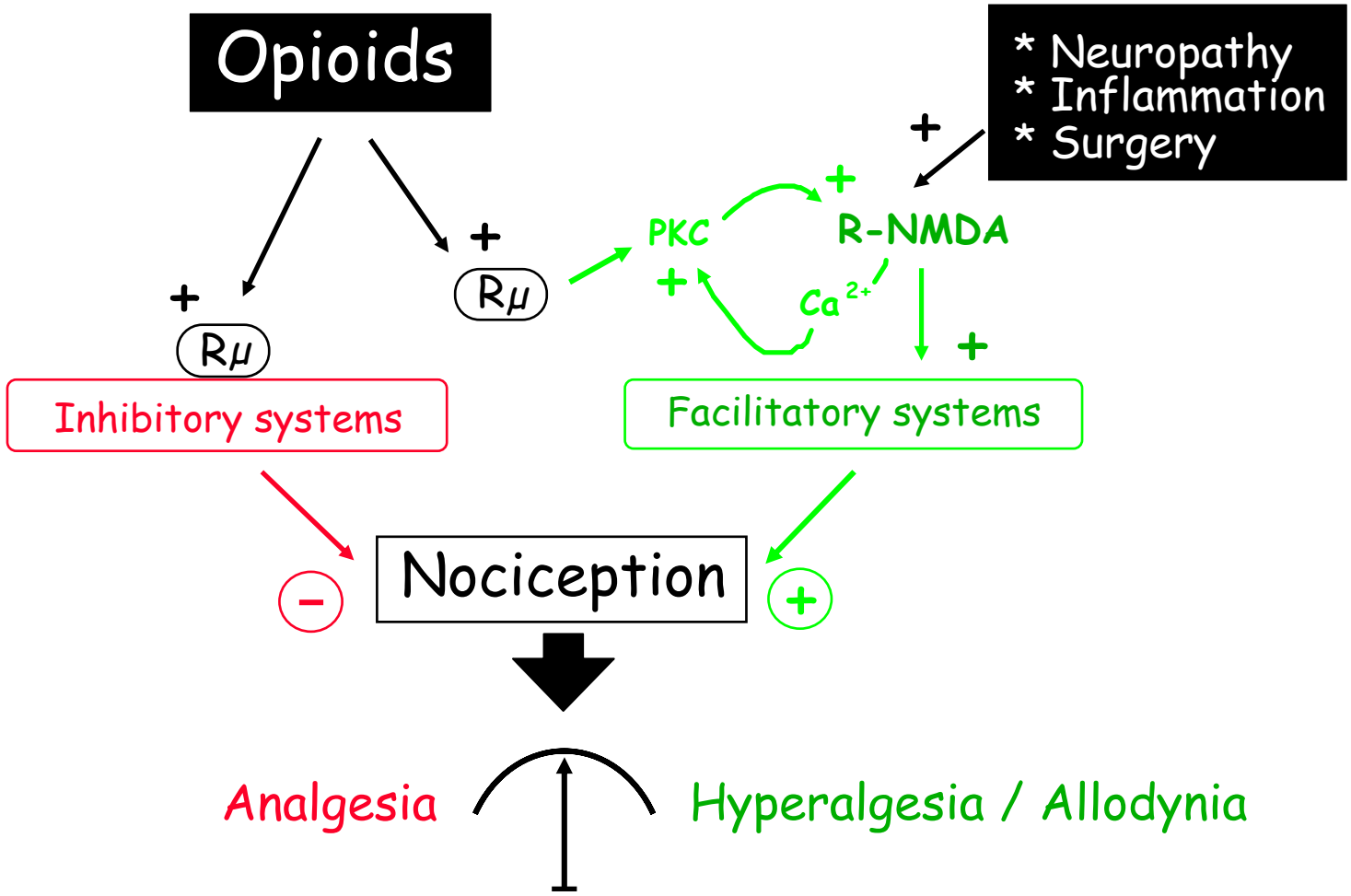
Dual effects of opioids: a neurobiological proposal



Short-lasting effects

Long-lasting effects

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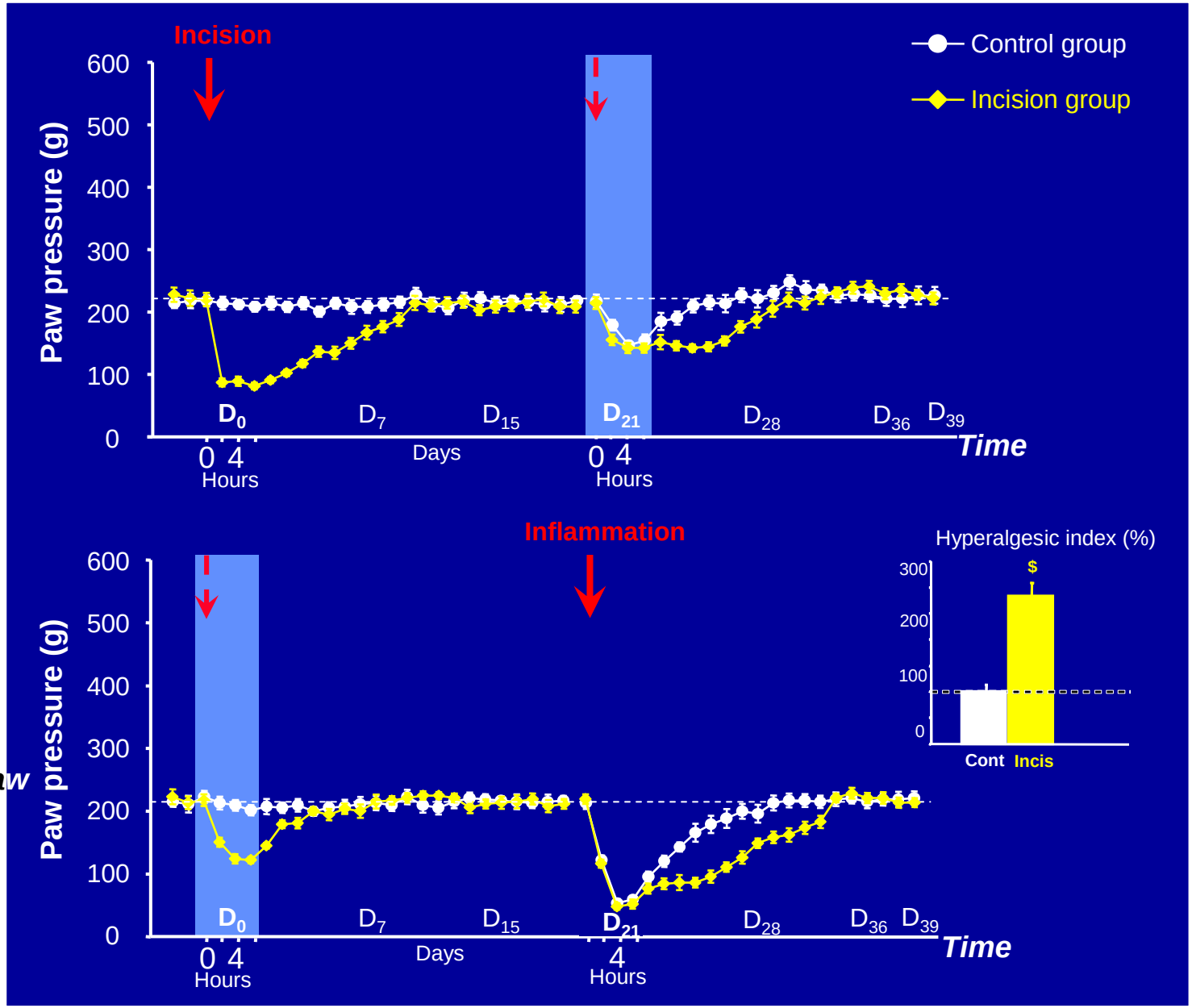
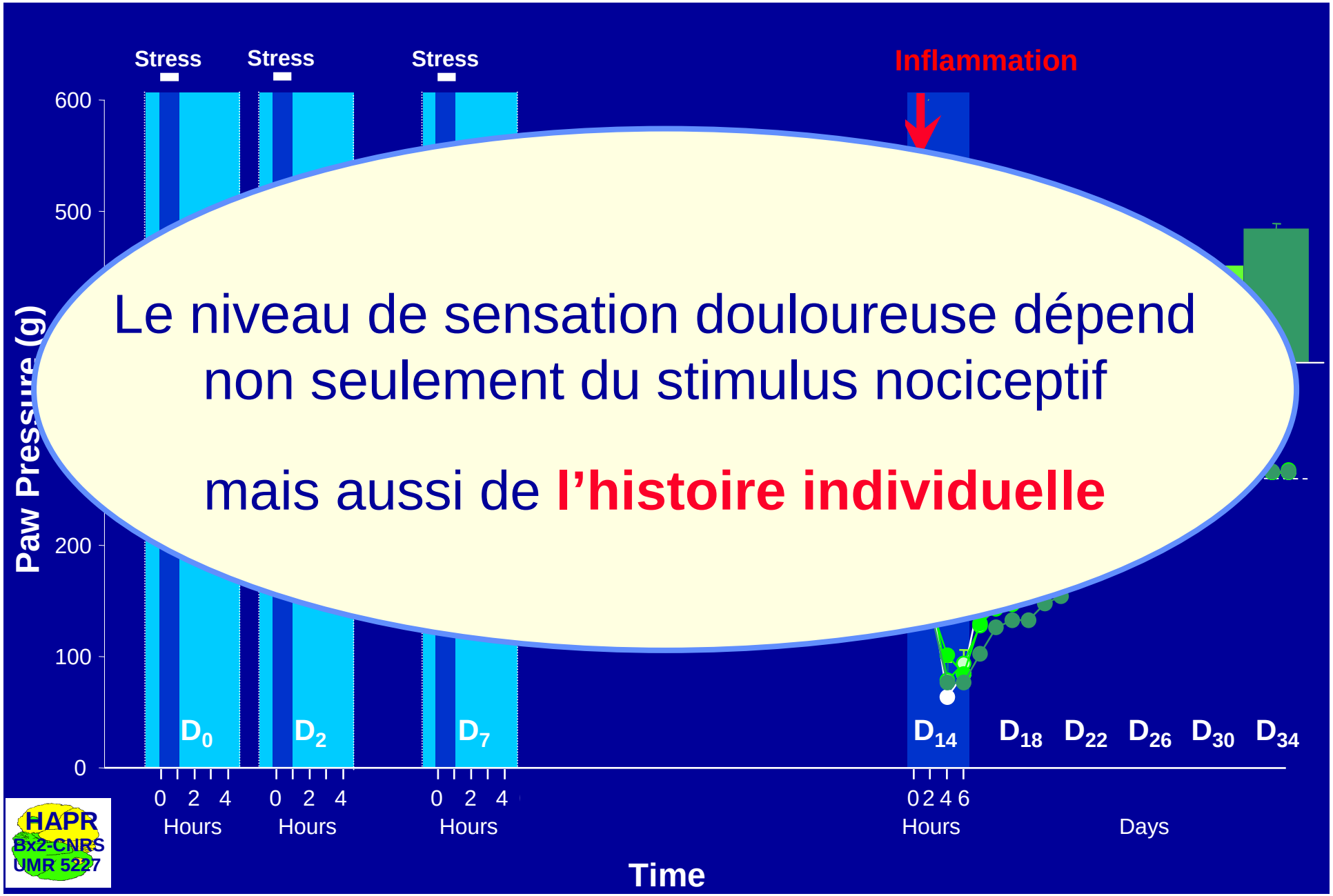
Paw pressure vocalization test

Incised hind paw

Non incised hind paw



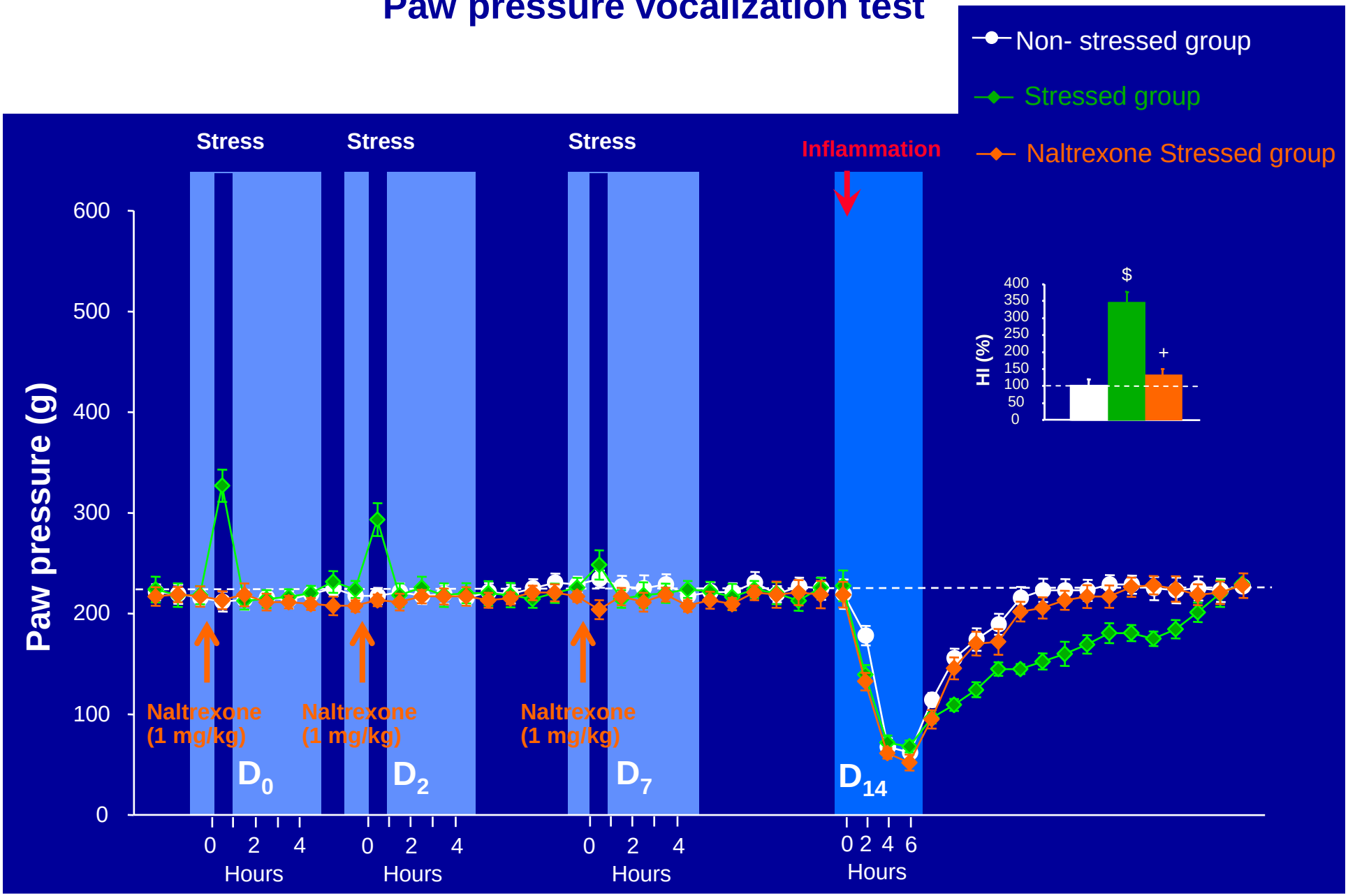
Dose-réponse stress / Patte ipsilatérale



Le niveau de sensation douloureuse dépend non seulement du stimulus nociceptif

mais aussi de **l'histoire individuelle**

Paw pressure vocalization test



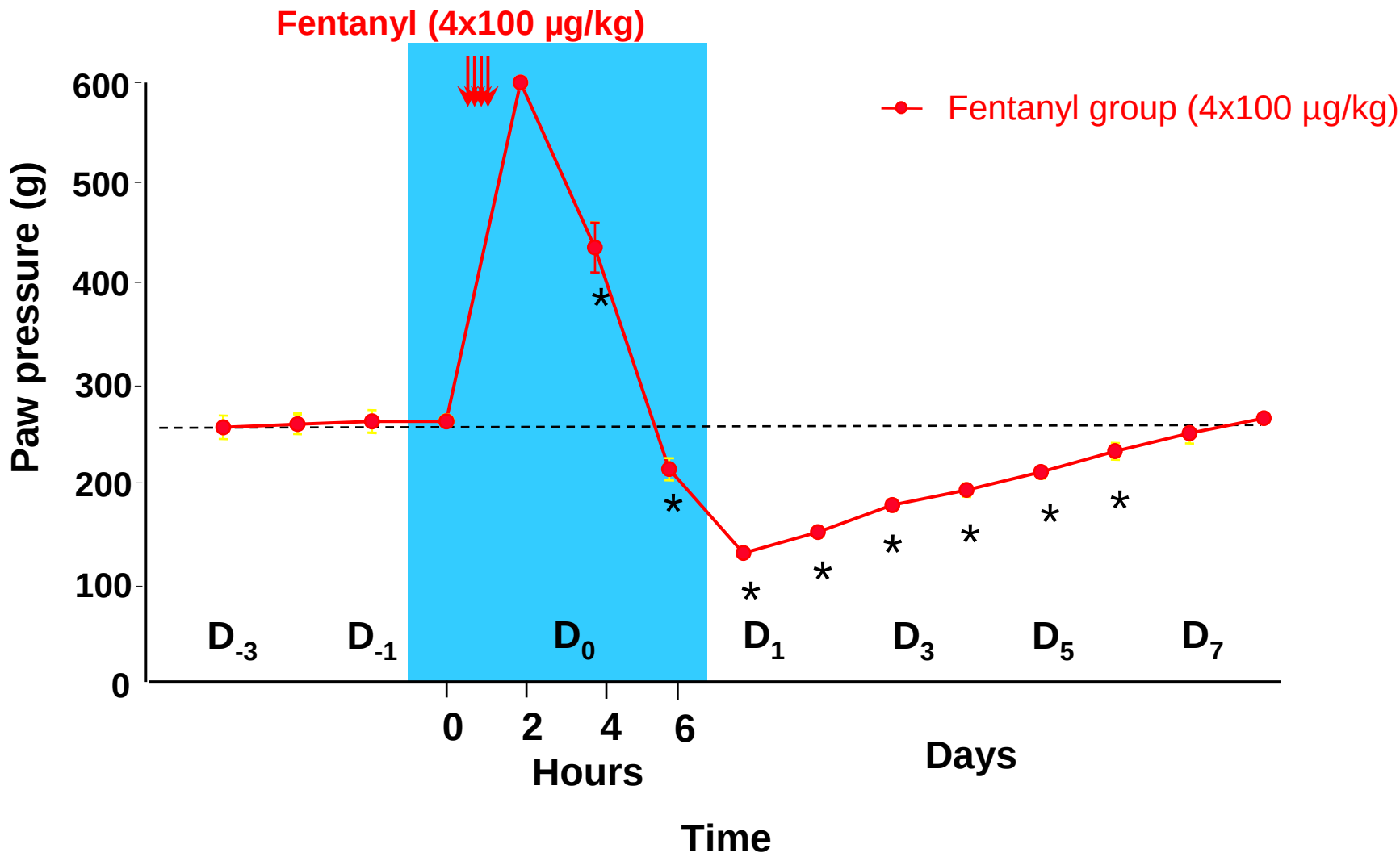
C. Le Roy et al. J. of Pain (in press)

Vulnérabilité à la douleur induit

par

une histoire douloureuse antérieure

Opioid induced hyperalgesia



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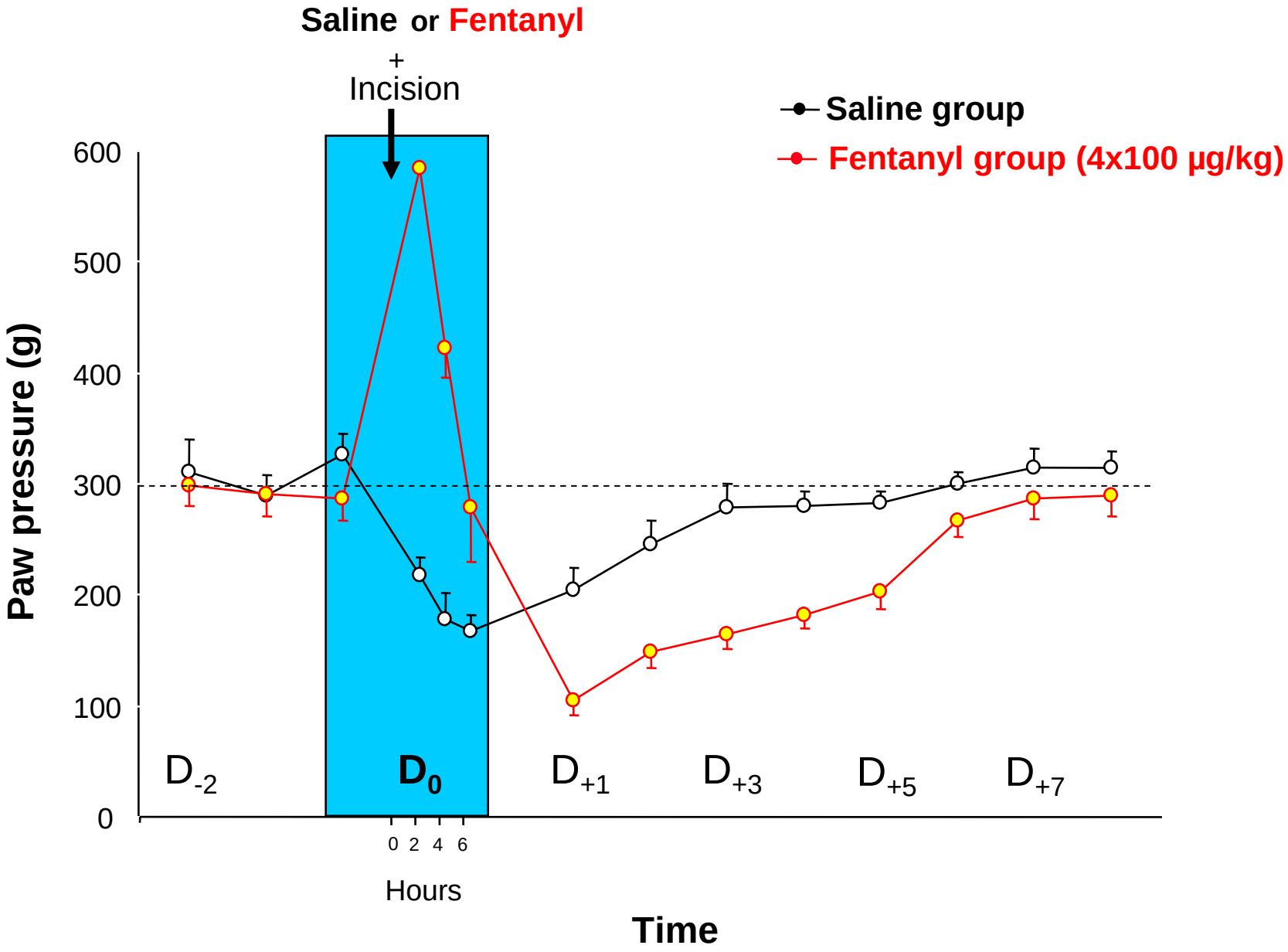
Incisional pain model



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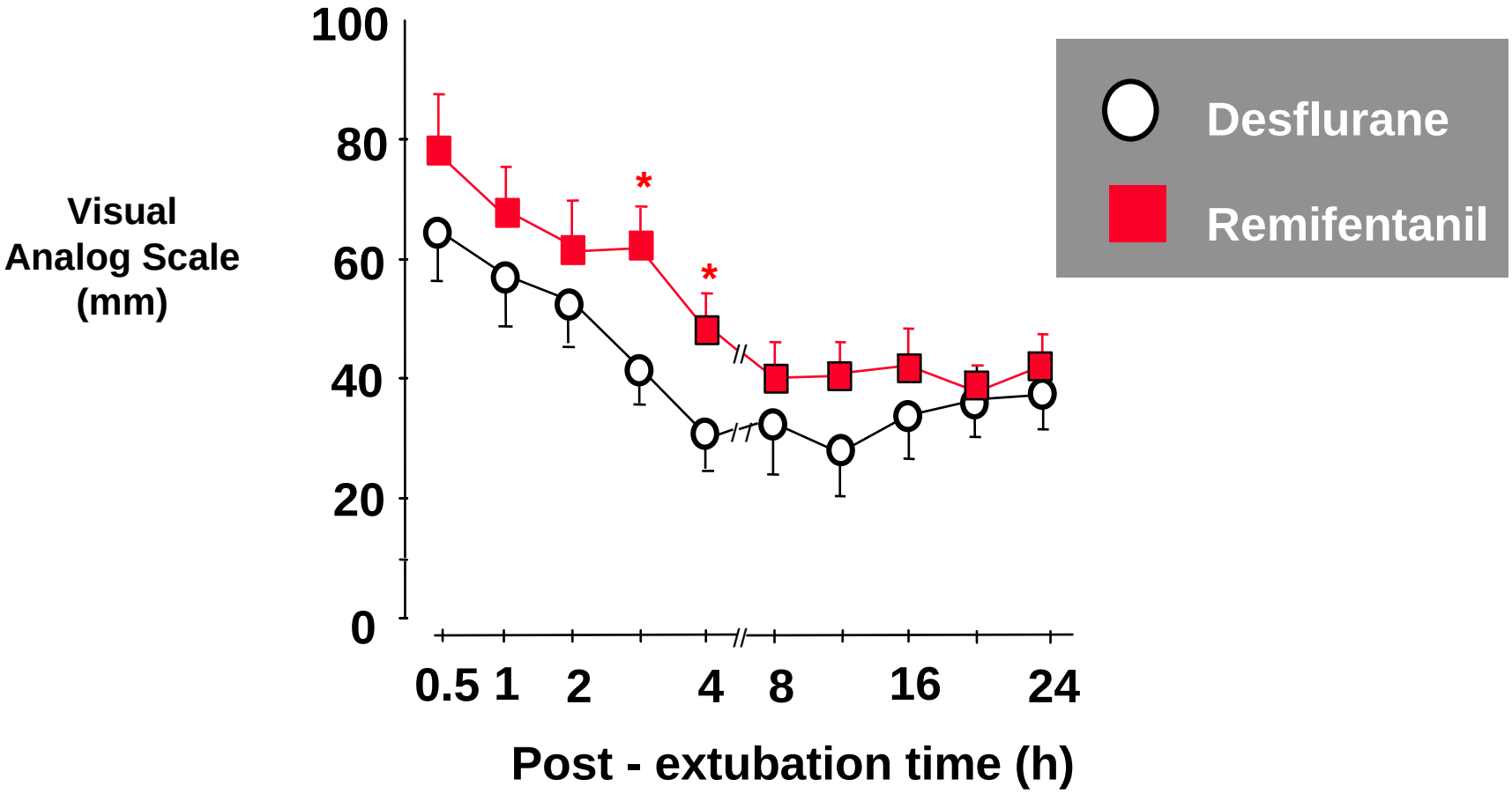
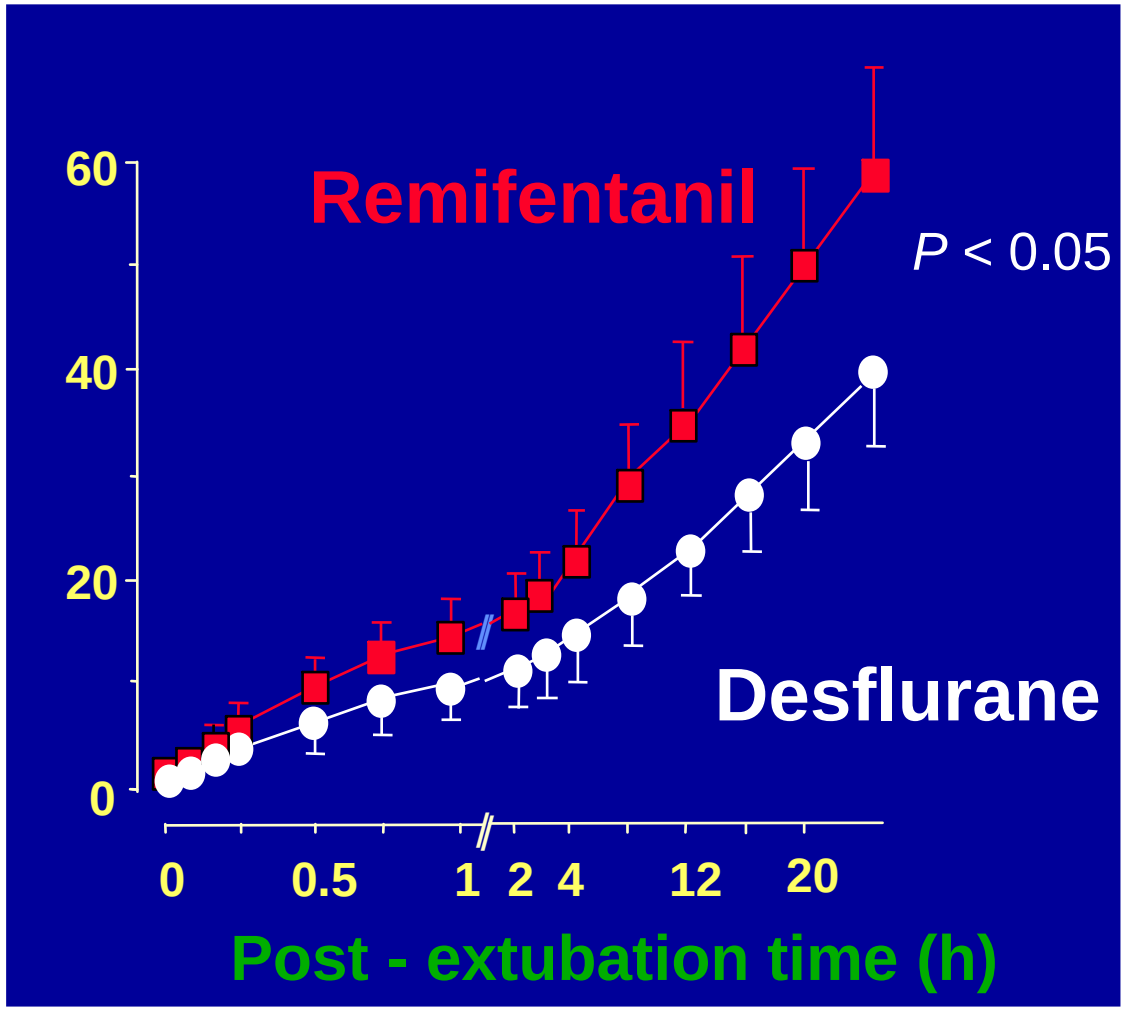
Visual analog scale pain scores (0-100 mm) in the two groups during the 24 hours after tracheal extubation



(mean ± 95% confidence interval)

*: *P* <0.05 vs desflurane

Remifentanil vs. desflurane based anesthesia

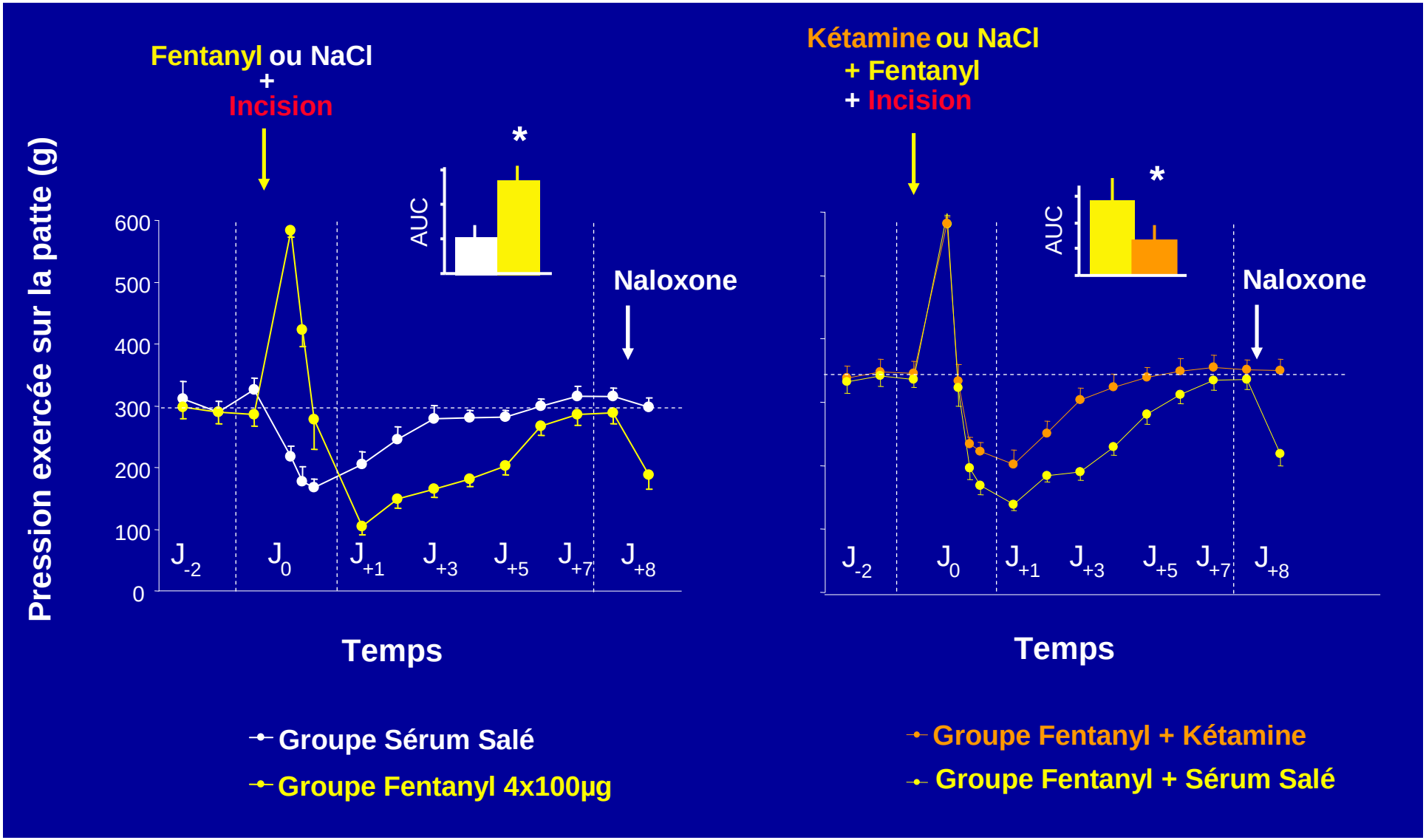


$P < 0.05$ vs. desflurane

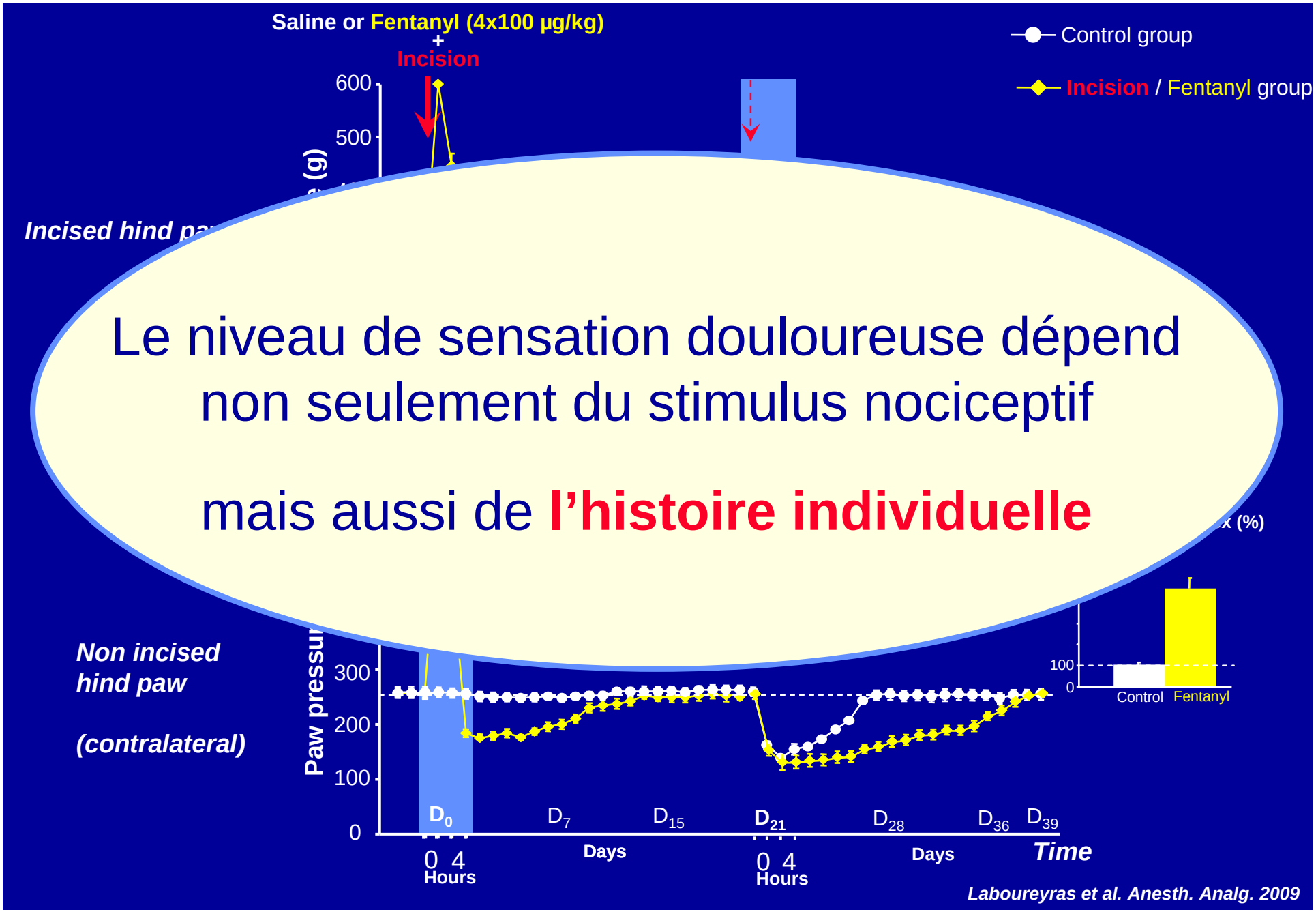
m ± 95% confidence interval

Guignard et al. Anesthesiology 2000; 93:409-17

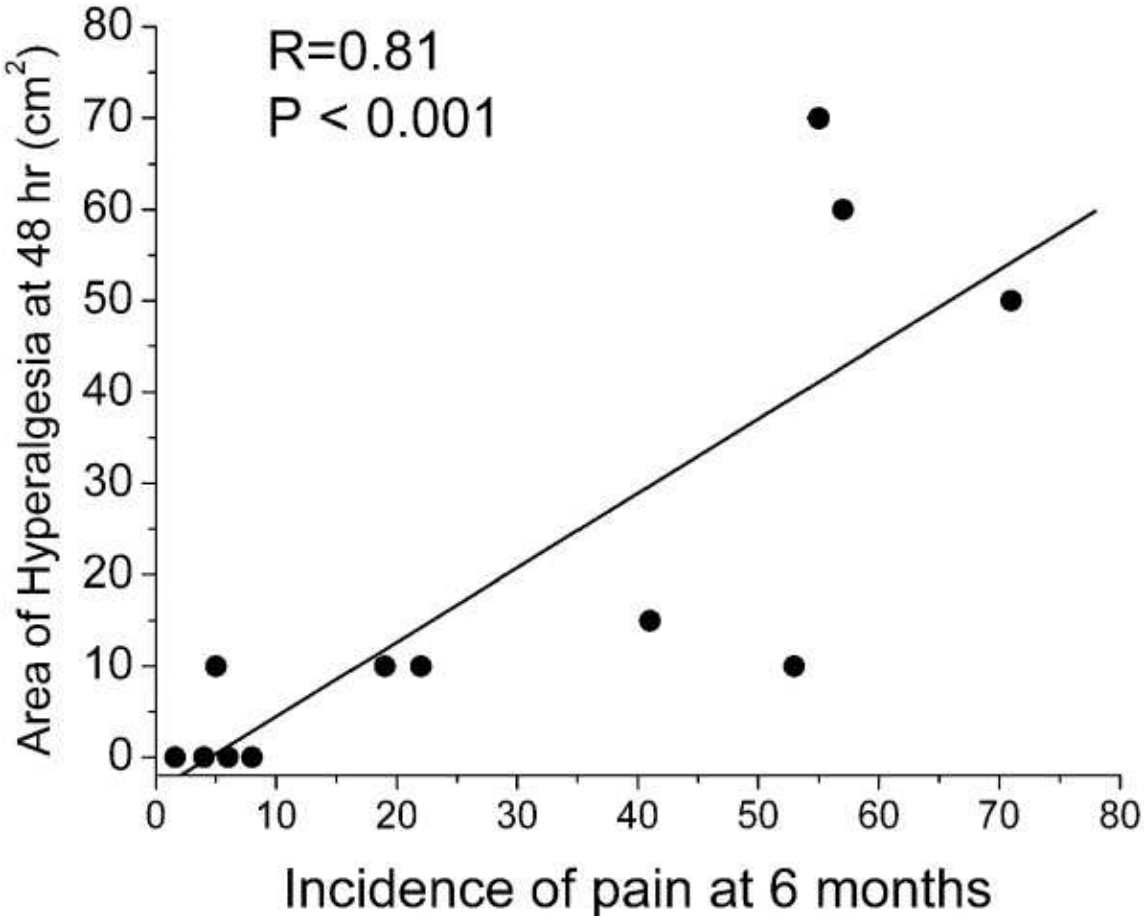
Opioid-induced hyperalgesia: an NMDA dependent phenomenon



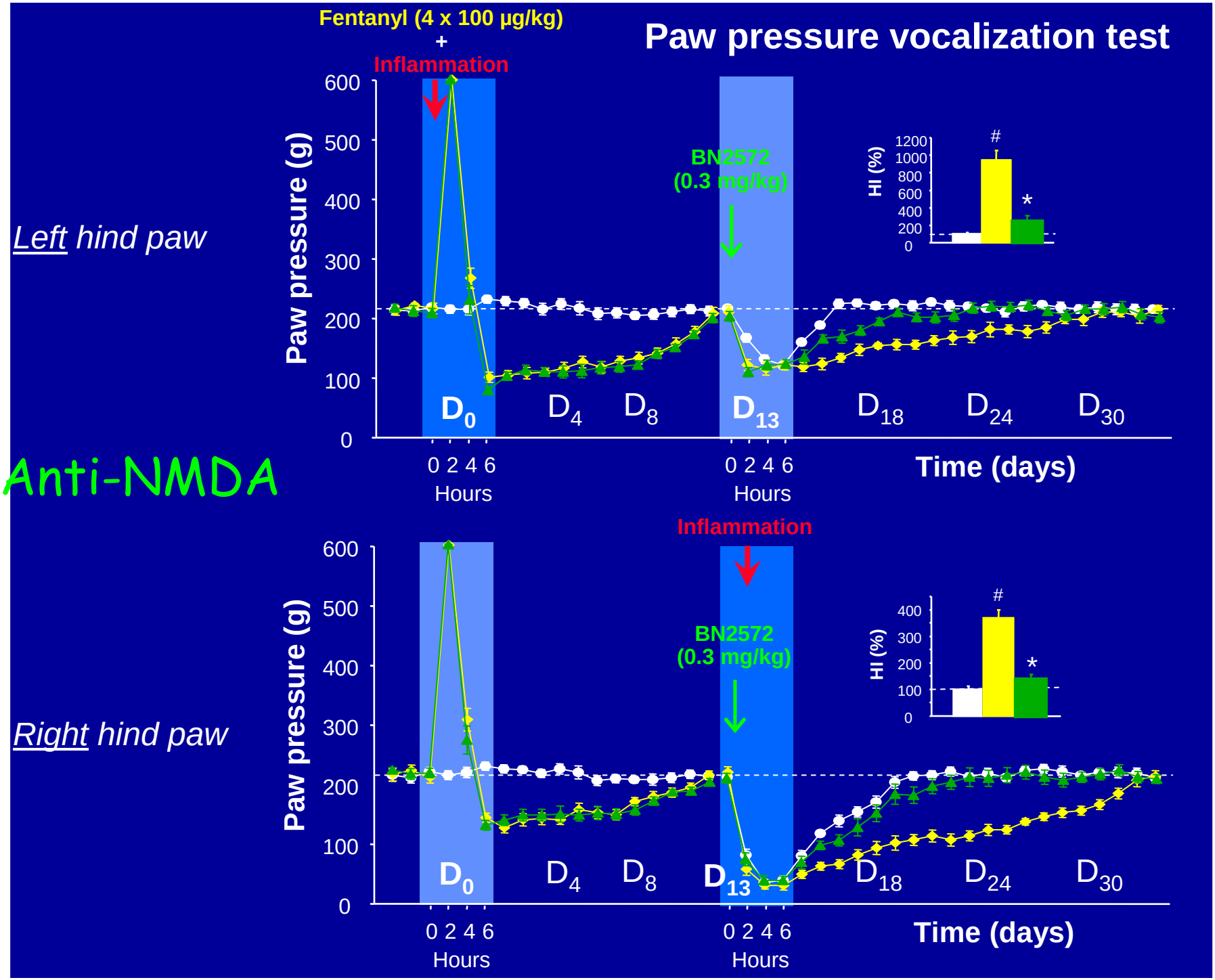
Paw pressure vocalization test



Relation surface d'hyperalgésie et douleur à 6 mois



Eisenach. Reg Anesth Pain Med 2006;31:1-3.


Fentanyl (4 x 100 µg/kg)
+
Inflammation
Paw pressure vocalization test
Left hind paw
Anti-NMDA
BN2572
(0.3 mg/kg)
Paw pressure (g)
HI (%)
D0
D4
D8
D13
D18
D24
D30
0 2 4 6
Hours
Time (days)
Right hind paw
Inflammation
BN2572
(0.3 mg/kg)

L'hypersensibilité à long terme facilitée

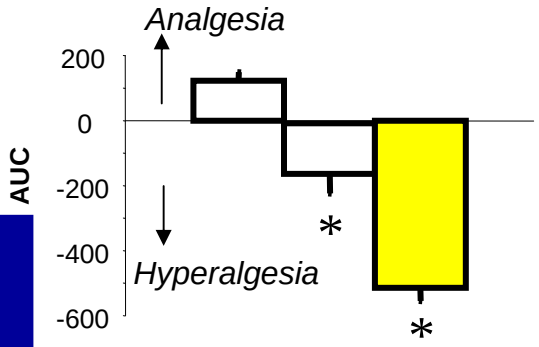
par les analgésiques opioïdes

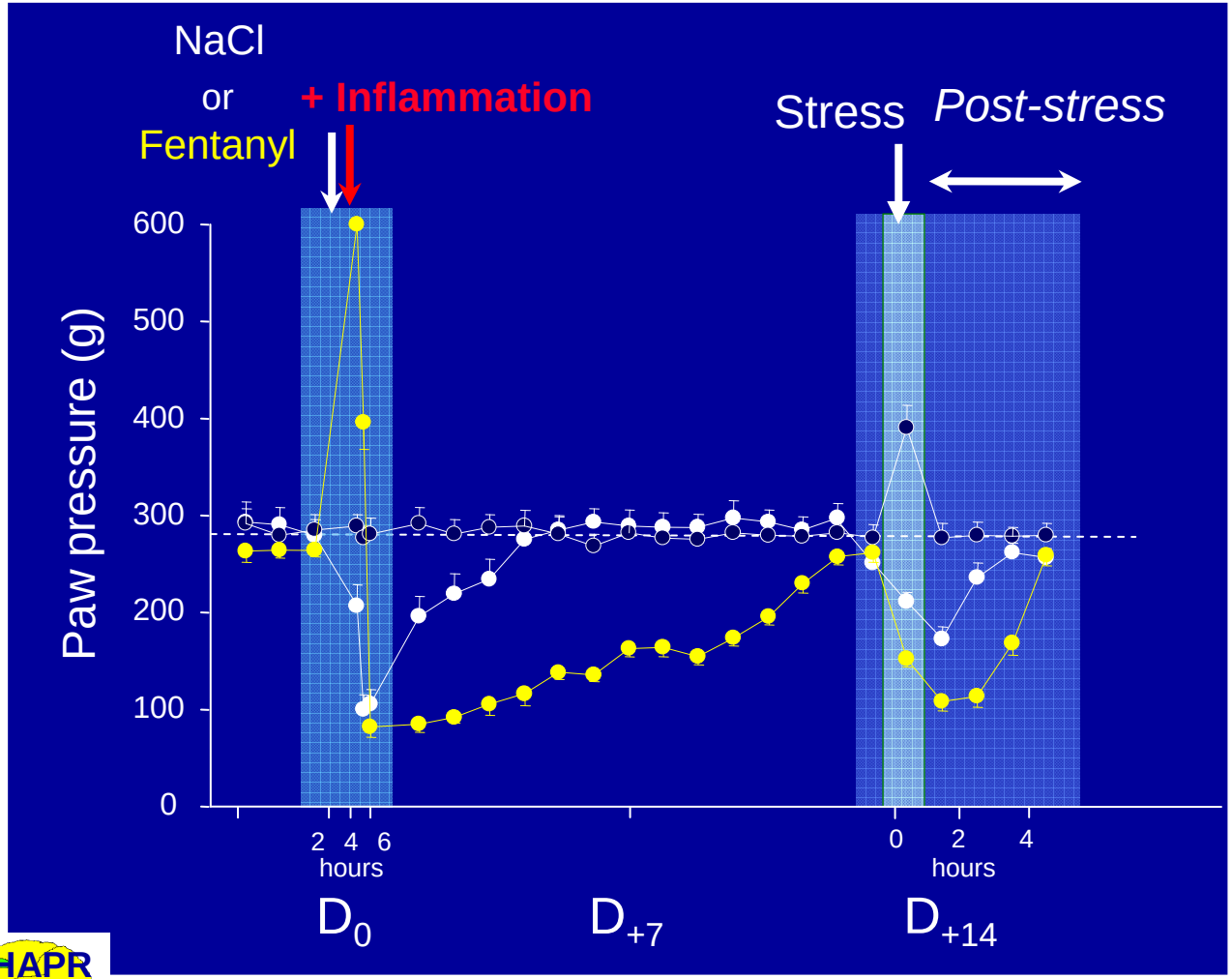
doit-elle nous inciter à supprimer

l'usage des substances opioïdes ?

NON !

Stress-induced analgesia or hyperalgesia ?





Time (days)

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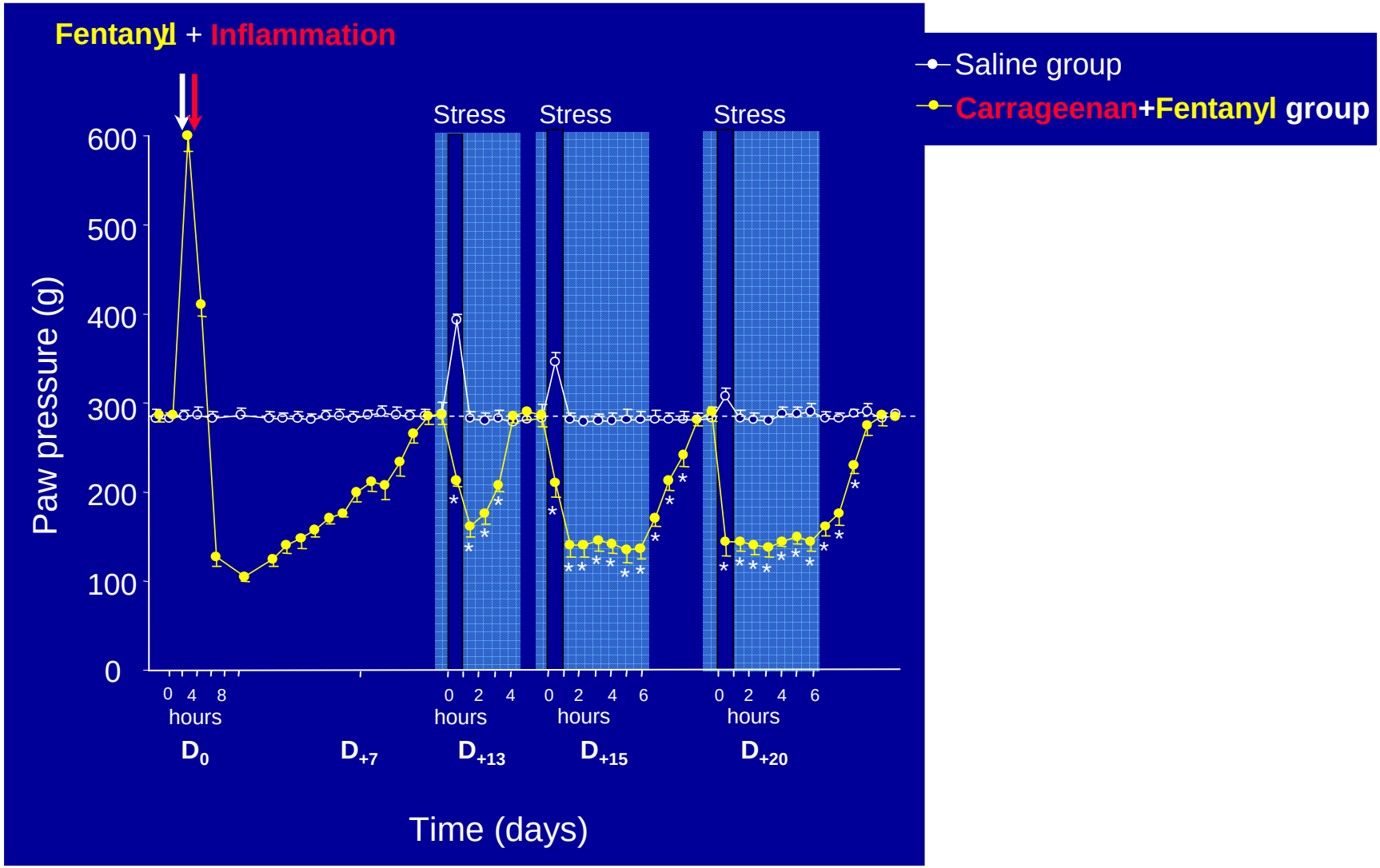
Rivat et al. Neuropsychopharmacology 2007

Repetitive stress



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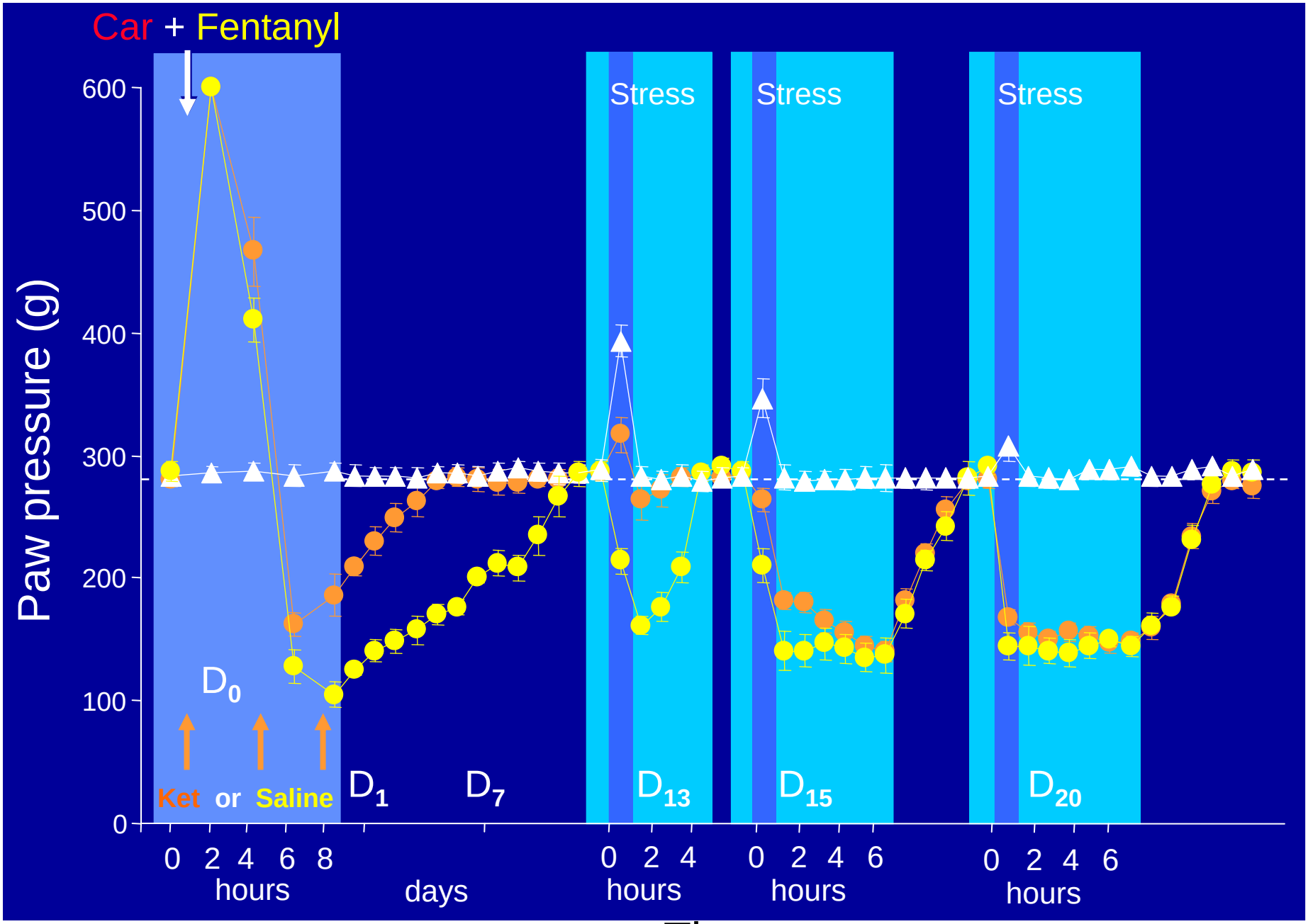
Rivat et al. Neuropsychopharmacology 2007



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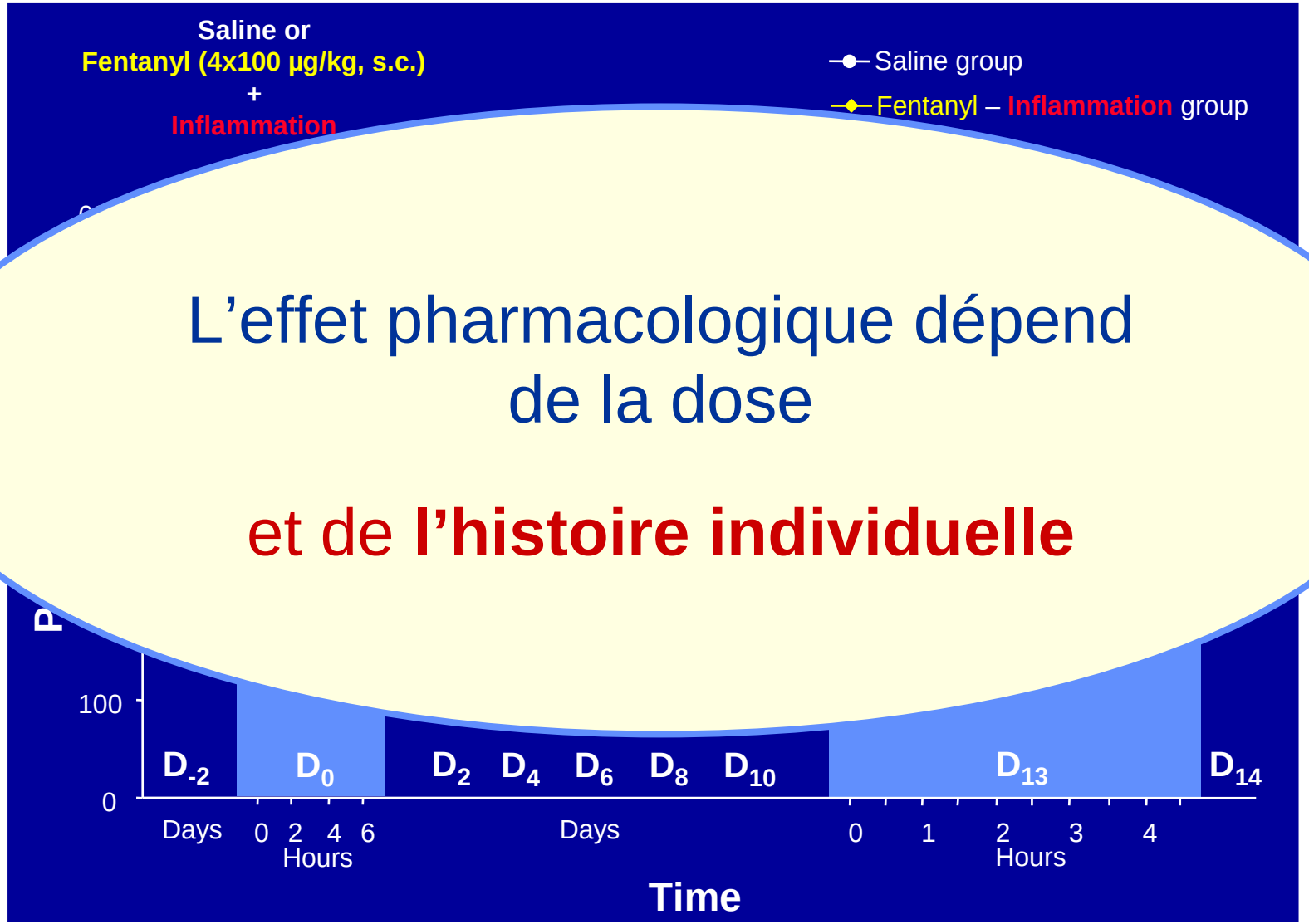
Rivat et al. Neuropsychopharmacology 2007

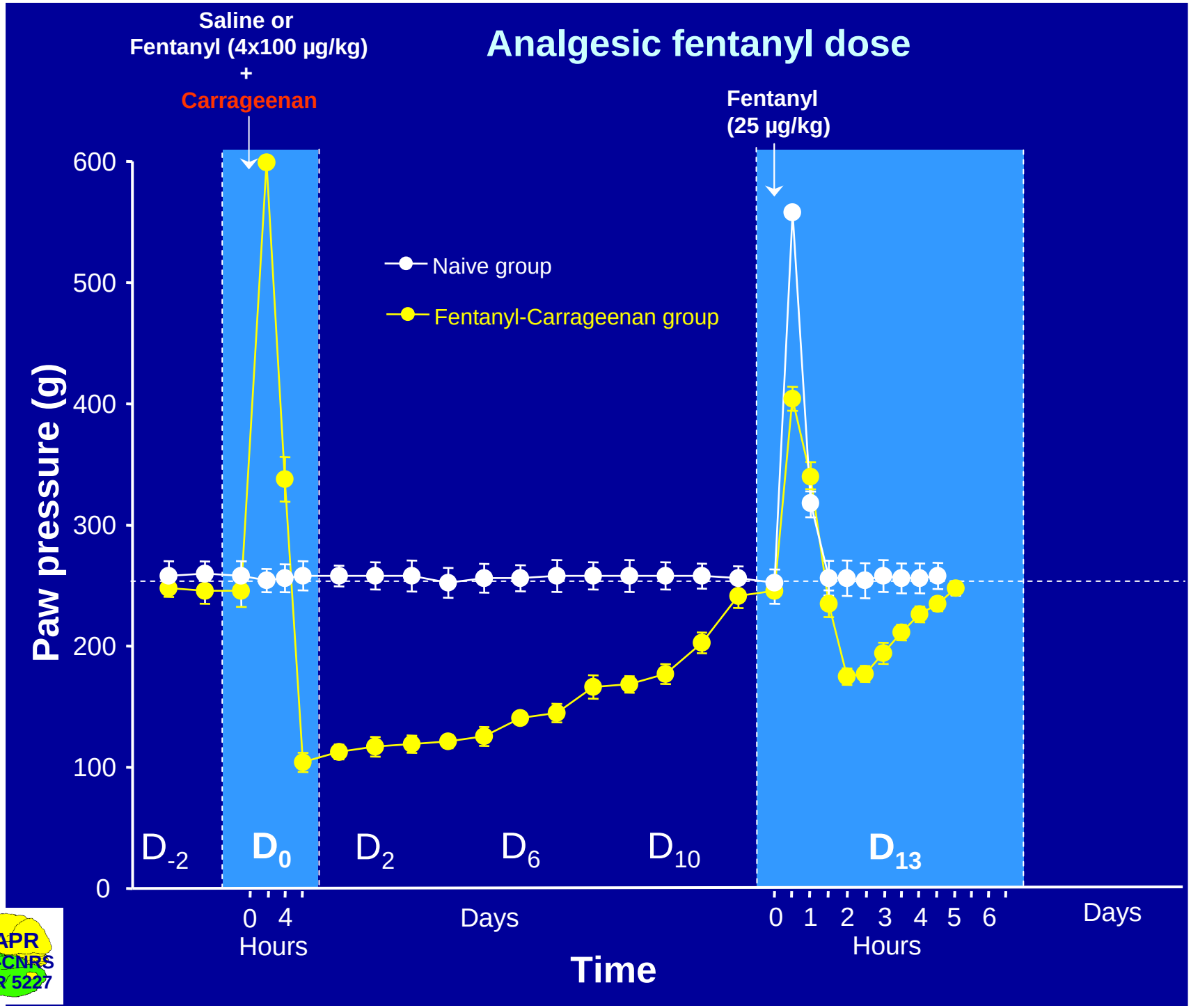
Fentanyl ultra-low dose



L'effet pharmacologique dépend de la dose

et de **l'histoire individuelle**

Rivat et al. Neuropsychopharmacology 2007


Analgesic fentanyl dose
Saline or
Fentanyl (4x100 µg/kg)
+
Carrageenan
Fentanyl
(25 µg/kg)
Naive group
Fentanyl-Carrageenan group
Paw pressure (g)
600
500
400
300
200
100
0
D-2
D0
D2
D6
D10
D13
0 4
Hours
Days
0 1 2 3 4 5 6
Hours
Days
Time
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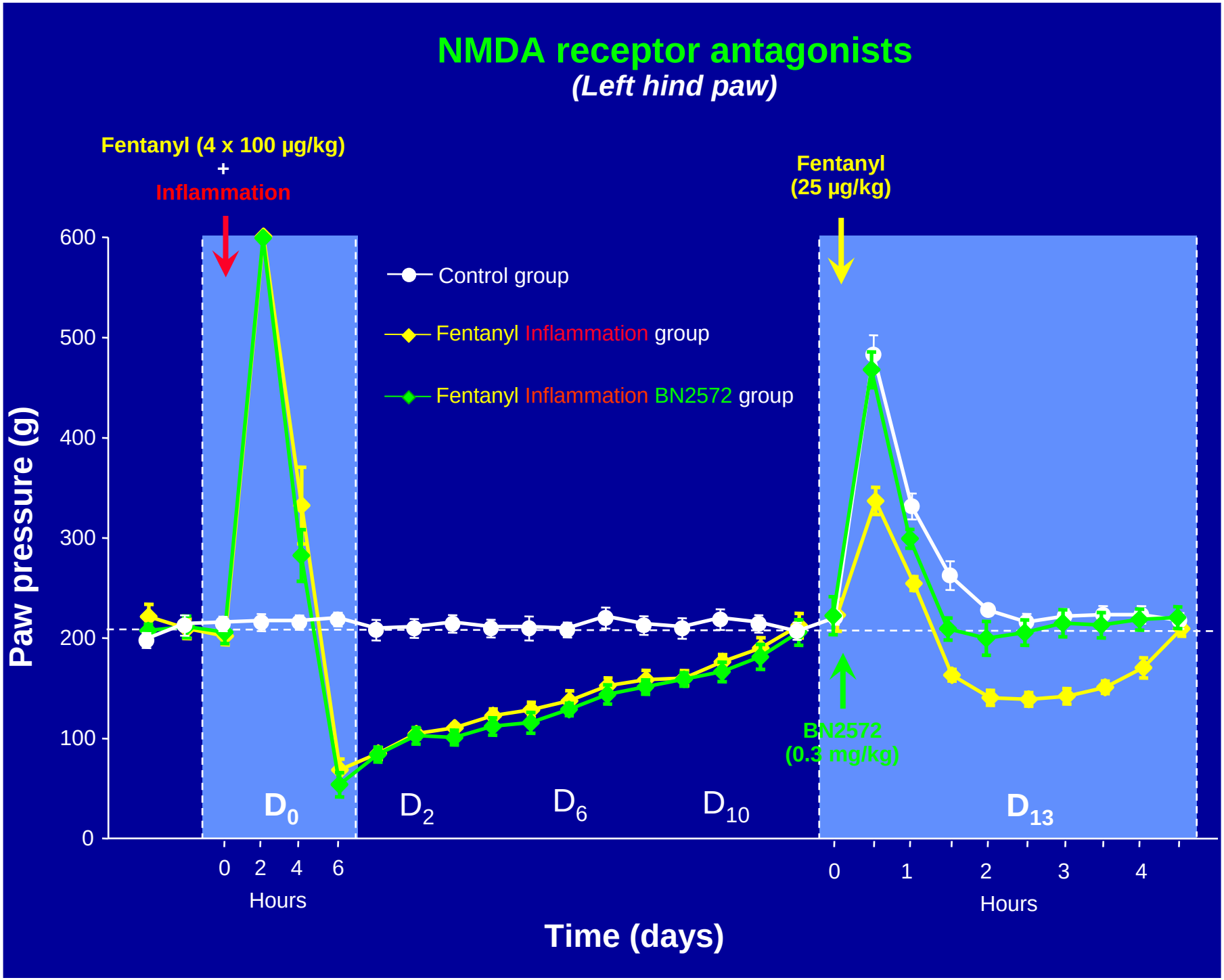
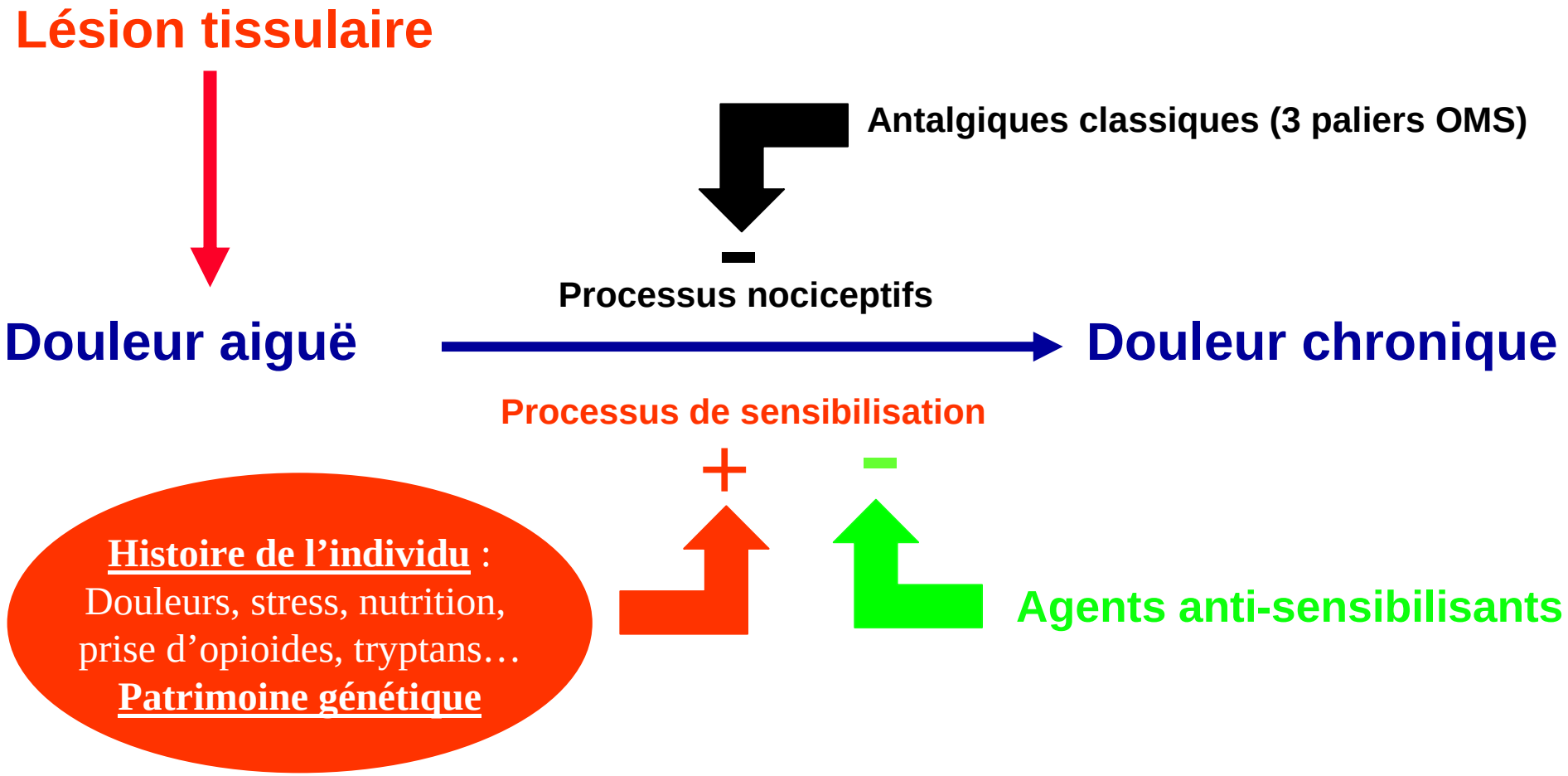

NMDA receptor antagonists
(Left hind paw)
Fentanyl (4 x 100 µg/kg)
+
Inflammation
Fentanyl
(25 µg/kg)
Control group
Fentanyl Inflammation group
Fentanyl Inflammation BN2572 group
Paw pressure (g)
600
500
400
300
200
100
0
BN2572
(0.3 mg/kg)
D0
D2
D6
D10
D13
0 2 4 6
Hours
0 1 2 3 4
Hours
Time (days)

Vers de nouvelles stratégies thérapeutiques ?

De la douleur aiguë à la douleur chronique



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Pour une nouvelle classification des antalgiques

- **Antalgiques purs (anti-nociceptifs)**
- **Antalgiques hyperalgésiques**
- **Anti-hyperalgésiques non antinociceptifs**
- **Antalgiques anti-hyperalgésiques**

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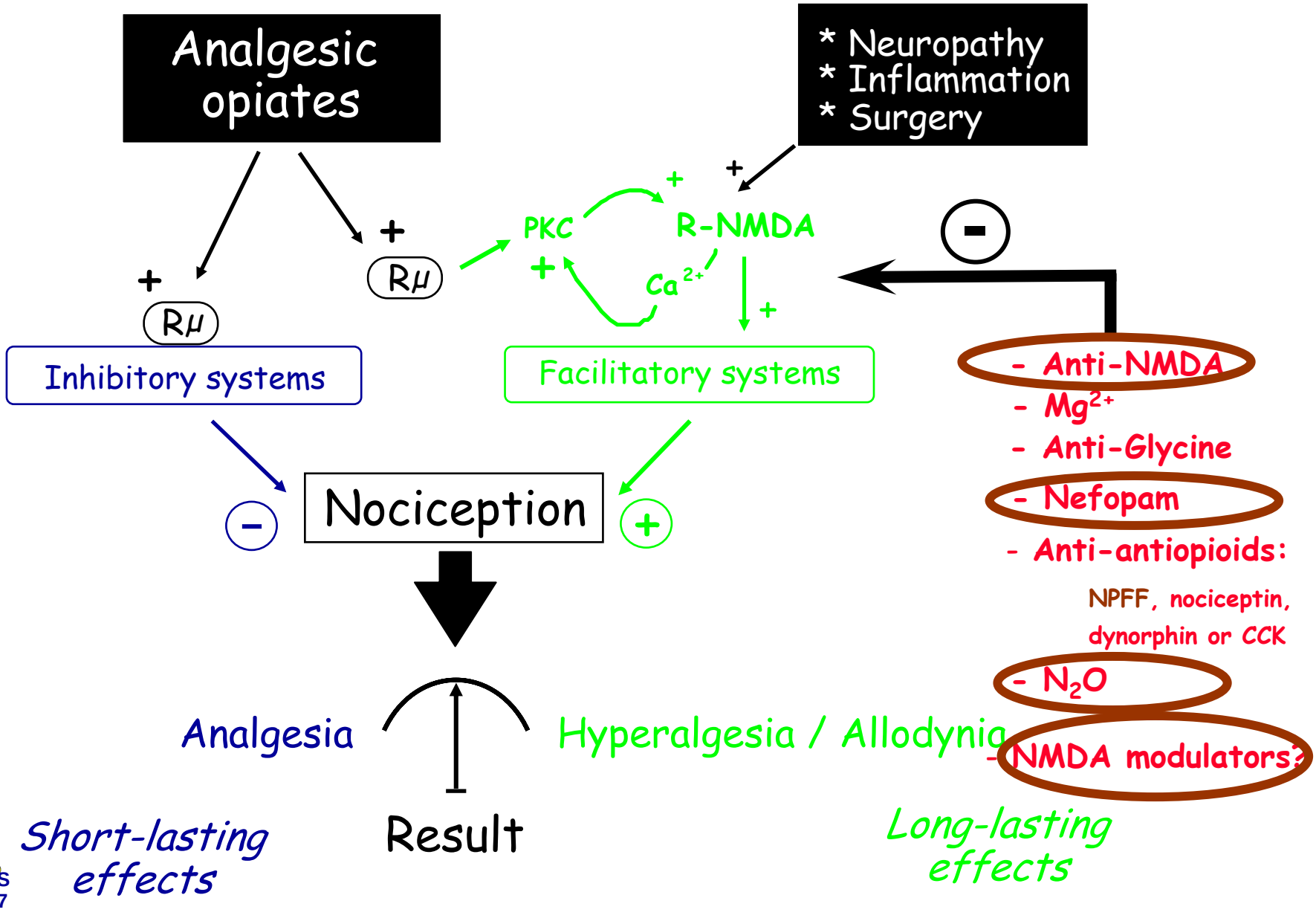
Pharmacological proposals



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Kétamine

(antagoniste NMDA)

Un anti-hyperalgésique, non antinociceptif

Anesthesiology
2000; 92:465–72

Long-lasting Hyperalgesia Induced by Fentanyl in Rats

Preventive Effect of Ketamine

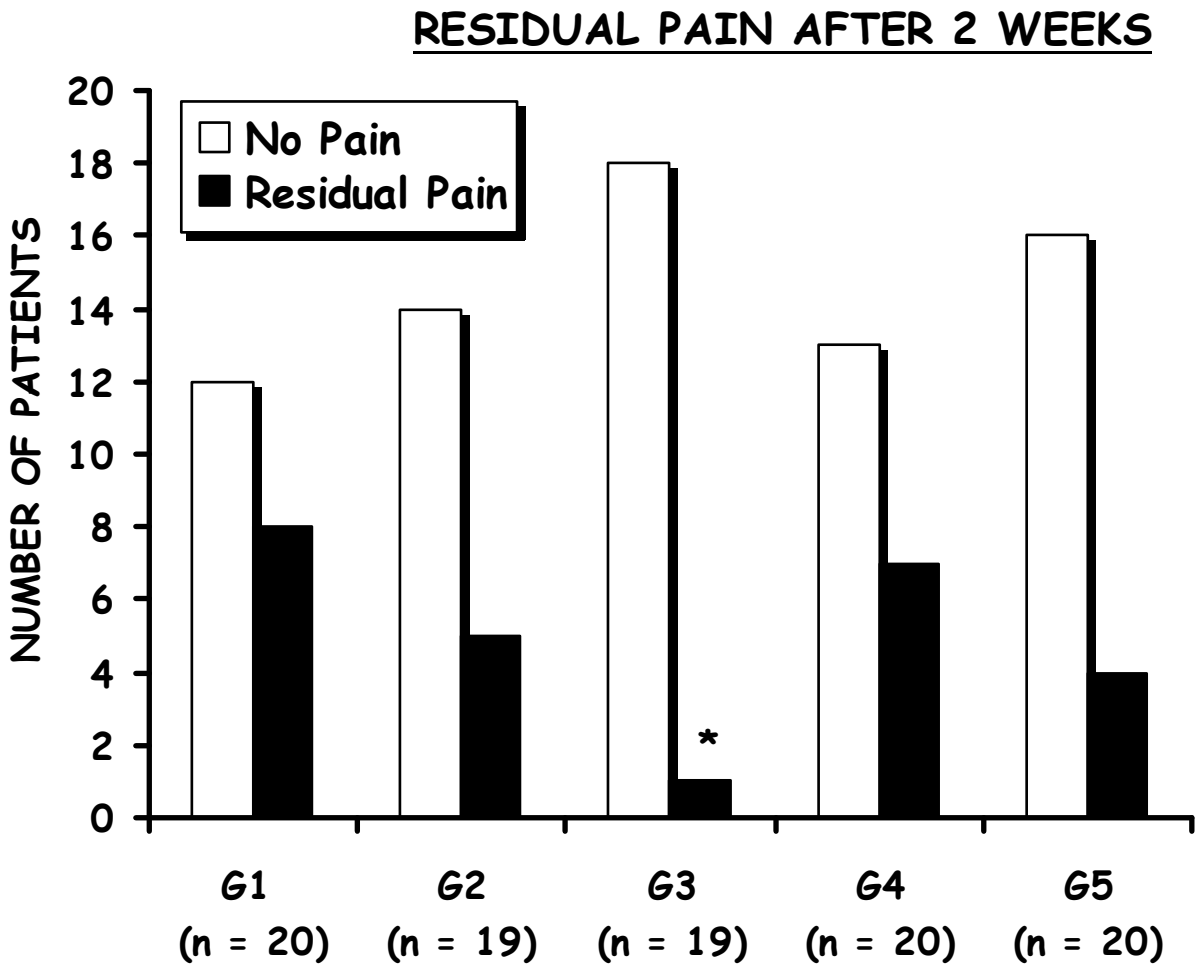
Evelyne Célèrier, Ph.D., Cyril Rivat, B.S.,* Yan Jun, M.D.,† Jean-Paul Laulin, Ph.D.,‡ Agnès Larcher, Ph.D.,§ Patrick Reynier, M.D.,‖ Guy Simonnet, Ph.D.#*

Anesthesiology 2005; 103:147–55

Remifentanil-induced Postoperative Hyperalgesia and Its Prevention with Small-dose Ketamine

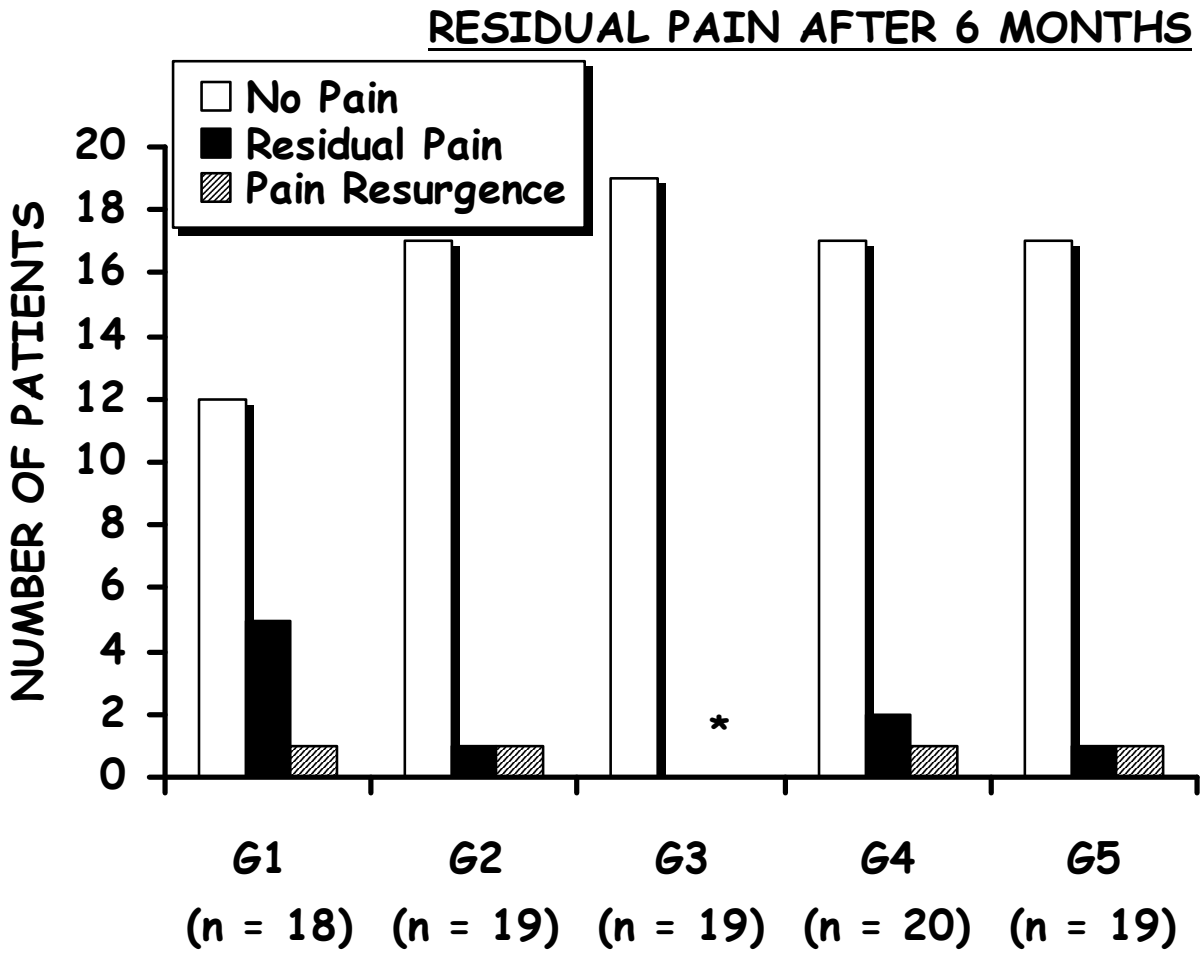
Vincent Joly, M.D., Philippe Richebe, M.D.,† Bruno Guignard, M.D.,* Dominique Fletcher, M.D.,‡ Pierre Maurette, M.D.,§ Daniel I. Sessler, M.D.,‖ Marcel Chauvin, M.D.#*

Long-term Effects of Ketamine on Analgesia



De Kock et al. Pain, 2001, 92: 373-380

Long-term Effects of Ketamine on Analgesia



De Kock et al. Pain, 2001, 92: 373-380

Protoxyde d’azote

(antagoniste NMDA)

Un « vieil » antinociceptif, anti-hyperalgésique

Preclinical data

Anesthesiology 2005; 103:845–54

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Nitrous Oxide Revisited

Evidence for Potent Antihyperalgesic Properties

Philippe Richebé, M.D., Ph.D.,* Cyril Rivat, Ph.D.,† Cyril Creton, M.Sc.,† Jean-Paul Lau
Pierre Maurette, M.D., Ph.D.,§ Marc Lemaire, M.D.,‖ Guy Simonnet, Ph.D.#

Background: Although opioids are unsurpassed analgesics for surgery, they also induce an *N*-methyl-D-aspartate–dependent enhancement of postoperative hyperalgesia. Because nitrous oxide (N_2O) has anti–*N*-methyl-D-aspartate properties, the purpose of this study was to evaluate nitrous oxide ability to

NITROUS oxide is co
relief. Experimental a
nitrous oxide induces
aqueductal brainstem

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ScienceDirect

Neuropharmacology 53 (2007) 733–740

NEURO PHARMACOLOGY

www.elsevier.com/locate/neuropharm

Nitrous oxide (N_2O) prevents latent pain sensitization and long-term anxiety-like behavior in pain and opioid-experienced rats☆

pe Richebé [a,b], Emilie Laboureyras [a], Jean-Paul Laulin [a],
elo Contarino [c], Guy Simonnet [a,*]

ux 2, Université Bordeaux 1, CNRS, UMR 5227, Bordeaux, France
Réanimation II, Centre Hospitalo-Universitaire de Bordeaux, Bordeaux, France
iversité Bordeaux 2, Unité de Nutrition et Neuroscience, Bordeaux, France
echerche Claude Delorme, Air Liquide, Jouy-en-Josas, France

07; received in revised form 31 July 2007; accepted 2 August 2007

The Journal of Pain, Vol 11, No 1 (January), 2010: pp 13-23
Available online at www.sciencedirect.com

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Original Reports

A Single Nitrous Oxide (N_2O) Exposure Leads to Persistent Alleviation of Neuropathic Pain in Rats

Baptiste Bessière,*† Emilie Laboureyras,* Jérémy Chateauraynaud,*
and Guy Simonnet*

*Université Bordeaux 2, Université Bordeaux 1, CNRS, UMR 5227, Bordeaux, France; and †
Delorme, Air Liquide, Jouy-en-Josas, France.

Abstract: Using the rat chronic constriction injury (CCI) pain model, we evalua
oxide (N_2O), a gas shown to have potent anti-hyperalgesic properties, may a
pain. Mechanical nociceptive threshold was estimated using the paw pressure vo
mal allodynia was challenged by measuring the struggle latency by immersion
a 10°C water bath. A single 50% N_2O exposure for 1 hour, 15 minutes not
anti-nociception during N_2O exposure but also provoked a delayed and sustai
to 46%) of pain hypersensitivity of the injured hind paw and abolished pain
the contralateral uninjured hind paw for at least 1 month. Thermal allodynia
vented by a single N_2O exposure. A preadministration of naltrexone, which ma
N_2O-induced anti-nociception, did not affect the persistent reduction of hypera
tration of naltrexone in N_2O-treated rats, 1 week after the gas exposure, did n
This suggests that the long-lasting effect of N_2O was not due to its prior ac
and was independent of endogenous opioid systems. These data suggest that
could be an efficient and safe strategy for alleviating neuropathic pain in a per
Perspective: *Because a single 50% N_2O exposure induced a persistent reduct
allodynia in a rat neuropathic pain model, clinical trials must be developed for
effects in patients with neuropathic pain. The ability of N_2O to potentiate analg
drugs also must be evaluated.*

© 2010 by the American Pain Society

Key words: *Nitrous oxide, neuropathic pain, hyperalgesia, central sensitization,*

Somatosensory systems, pain 1167

Xenon prevents inflammation-induced delayed pain hypersensitivity in rats

Baptiste Bessière[a,b], Emilie Laboureyras[a], Jean-Paul Laulin[a]
and Guy Simonnet[a]

Rats received an intraplantar carrageenan injection for inducing hind paw inflammation. After 1 h 45 min, they were exposed to medical air (air group), xenon 25% (Xe-25 group) or 50% (Xe-50 group) for 1 h 45 min. Mechanical nociceptive threshold was evaluated on experimental day and once daily for 1 week. Beyond the well-known antinociceptive effect of xenon, the delayed hyperalgesia observed for 4 days after carrageenan injection was strongly reduced in Xe-25 group and totally suppressed in Xe-50 group on the inflamed hind paw. Moreover, delayed hyperalgesia on the noninflamed hind paw was totally suppressed for both the xenon concentrations. These results show that xenon, beyond its antinociceptive effects, may be a fruitful therapeutic strategy to limit the development of pain sensitization after tissue injury. *NeuroReport* 21:1167–1171 © 2010 Wolters Kluwer Health | Lippincott Williams & Wilkins.

NeuroReport 2010, 21:1167–1171

Keywords: hyperalgesia, inflammation, pain sensitization, xenon

[a]Université Bordeaux 2, Université Bordeaux 1, CNRS, Bordeaux and [b]Centre de Recherche Claude Delorme, Air Liquide, Jouy-en-Josas, France

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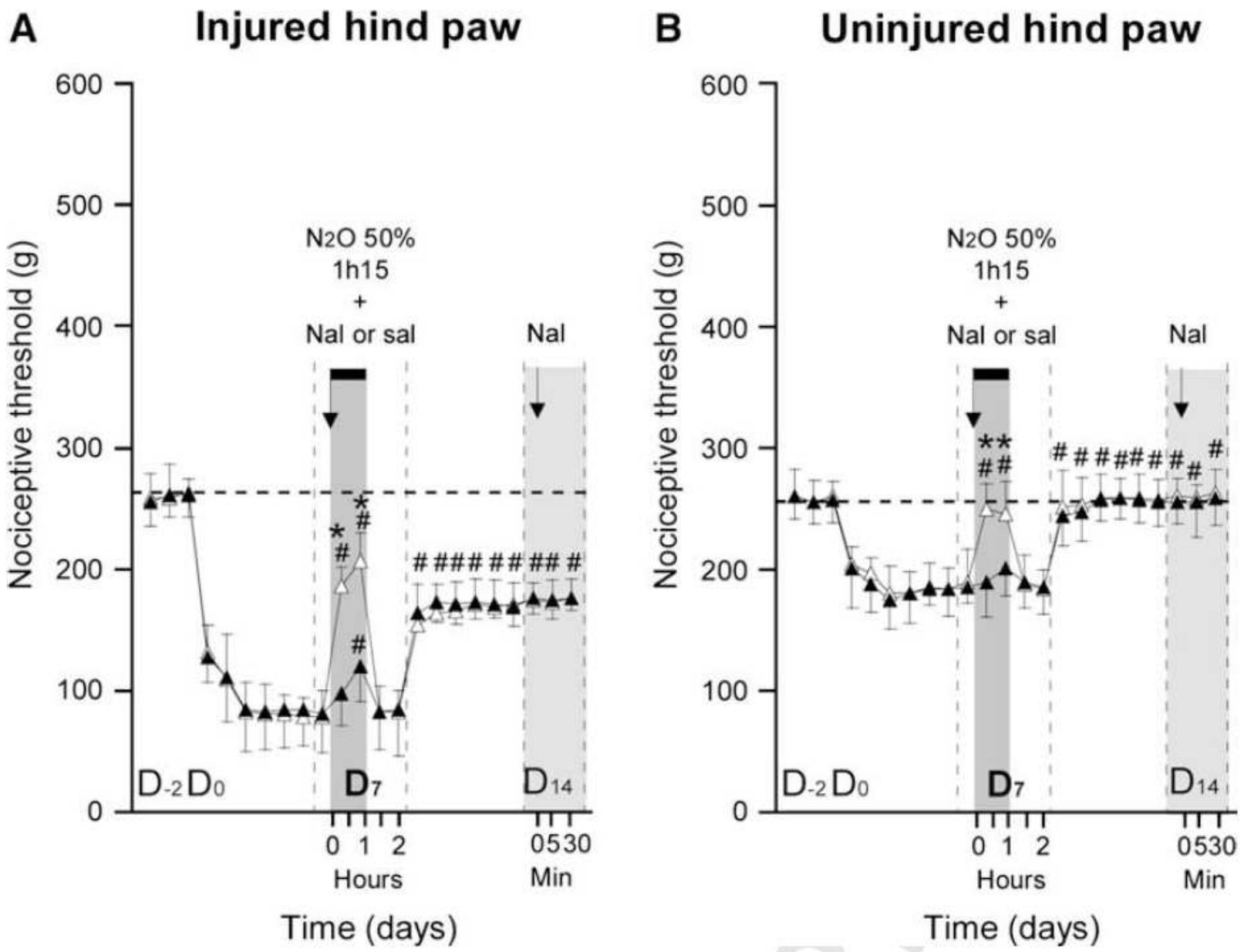
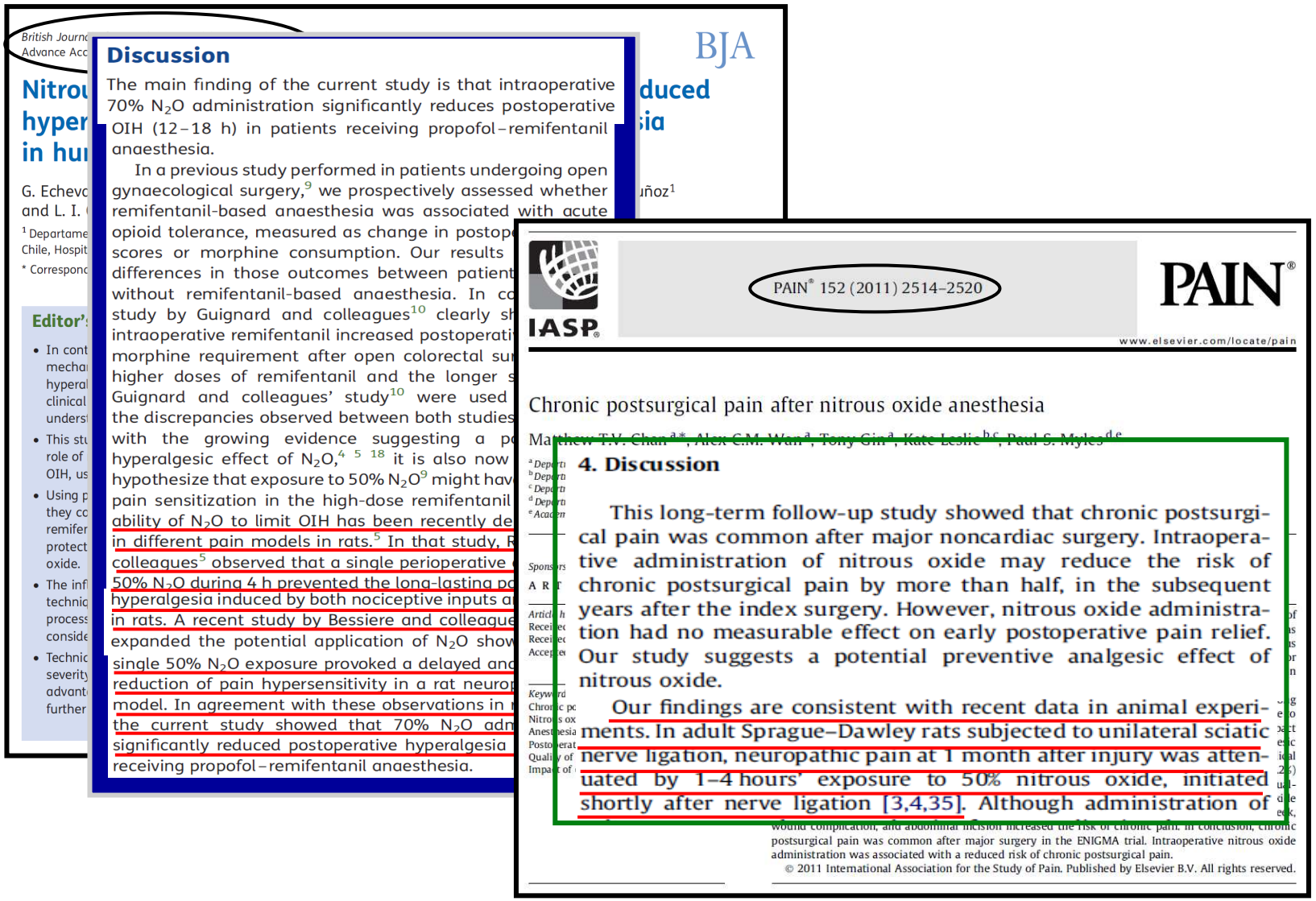
Tel: +33 13 907 6522; fax: +33 13 907 6199;
e-mail: baptiste.bessiere@airliquide.com

Received 20 September 2010 accepted 23 September 2010



Bessiere et al. J. of Pain, 2009

Clinical data



Discussion

The main finding of the current study is that intraoperative 70% N_2O administration significantly reduces postoperative OIH (12–18 h) in patients receiving propofol–remifentanil anaesthesia.

In a previous study performed in patients undergoing open gynaecological surgery,[9] we prospectively assessed whether remifentanil-based anaesthesia was associated with acute opioid tolerance, measured as change in postop scores or morphine consumption. Our results differences in those outcomes between patient without remifentanil-based anaesthesia. In co study by Guignard and colleagues[10] clearly sh intraoperative remifentanil increased postoperati morphine requirement after open colorectal su higher doses of remifentanil and the longer s Guignard and colleagues' study[10] were used the discrepancies observed between both studies with the growing evidence suggesting a po hyperalgesic effect of N_2O,[4 5 18] it is also now hypothesize that exposure to 50% N_2O[9] might hav pain sensitization in the high-dose remifentanil ability of N_2O to limit OIH has been recently de in different pain models in rats.[5] In that study, R colleagues[5] observed that a single perioperative 50% N_2O during 4 h prevented the long-lasting po hyperalgesia induced by both nociceptive inputs a in rats. A recent study by Bessiere and colleague expanded the potential application of N_2O show single 50% N_2O exposure provoked a delayed and reduction of pain hypersensitivity in a rat neurop model. In agreement with these observations in r the current study showed that 70% N_2O adm significantly reduced postoperative hyperalgesia receiving propofol–remifentanil anaesthesia.

BJA

PAIN® 152 (2011) 2514–2520

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IASP

Chronic postsurgical pain after nitrous oxide anesthesia

4. Discussion

This long-term follow-up study showed that chronic postsurgical pain was common after major noncardiac surgery. Intraoperative administration of nitrous oxide may reduce the risk of chronic postsurgical pain by more than half, in the subsequent years after the index surgery. However, nitrous oxide administration had no measurable effect on early postoperative pain relief. Our study suggests a potential preventive analgesic effect of nitrous oxide.

Our findings are consistent with recent data in animal experiments. In adult Sprague–Dawley rats subjected to unilateral sciatic nerve ligation, neuropathic pain at 1 month after injury was attenuated by 1–4 hours' exposure to 50% nitrous oxide, initiated shortly after nerve ligation [3,4,35]. Although administration of

wound complication, and abdominal incision increased the risk of chronic pain. In conclusion, chronic postsurgical pain was common after major surgery in the ENIGMA trial. Intraoperative nitrous oxide administration was associated with a reduced risk of chronic postsurgical pain.

Néfopam

Un antinociceptif, anti-hyperalgésique

Long-Term Pain Vulnerability After Surgery in Rats: Prevention by Nefopam, an Analgesic with Antihyperalgesic Properties

Emilie Laboureyras, MSc*

Jeremy Chateauraynaud, MSc*

Philippe Richebé, MD, PhD*†

Guy Simonnet, PhD*

BACKGROUND: Tissue damage associated with surgery often produces peripheral and central sensitization that may outlast the stimuli, leading to exaggerated postoperative pain. Paradoxically, the use of opioid analgesia, which is essential for surgical pain management may induce pain sensitization leading to enhanced postoperative pain and an increased risk of developing chronic pain. We studied whether a surgical incision in the rat hindpaw may favor the development of long-term pain vulnerability by estimating hyperalgesia induced by an inflammatory stimulation of the unlesioned contralateral hindpaw 3 wk later. We also evaluated the ability of nefopam, an analgesic drug commonly used in postoperative pain management, to prevent not only exaggerated postoperative pain but also long-term pain vulnerability. The efficacy of morphine was assessed 1 day after surgical incision.

METHODS: On Day 0, a surgical plantar incision was performed in one hindpaw of rats treated or untreated with fentanyl ($4 \times 100\ \mu g/kg$, one injection every 15 min). Nefopam (10 mg/kg) or saline was subcutaneously injected 30 min before injury. Three weeks later, once pain measures had returned to basal values, a subsequent nociceptive stimulus, specifically intraplantar carrageenan injection, was performed to evaluate pain sensitivity in incision- and fentanyl-experienced rats. Pain was measured by the paw-pressure vocalization test and the weight bearing test.

RESULTS: Surgical incision in rats induced latent and long-term pain hypersensitivity, which was manifested by exaggerated hyperalgesia on carrageenan injection. Administering fentanyl in association with the surgical incision induced exaggerated postoperative pain. When injected before incision, nefopam reduced the exaggerated postoperative pain induced by perioperative fentanyl treatment and prevented the development of long-term pain hypersensitivity. Preoperative nefopam administration also improved morphine analgesic efficacy in the context of fentanyl-induced postoperative hyperalgesia.

CONCLUSIONS: Given preemptively, nefopam may be effective at improving postoperative pain management and at reducing the risk of developing postoperative chronic pain, because the drug has both analgesic and antihyperalgesic properties.

(Anesth Analg 2009;X:●●●–●●)

Gabapentine

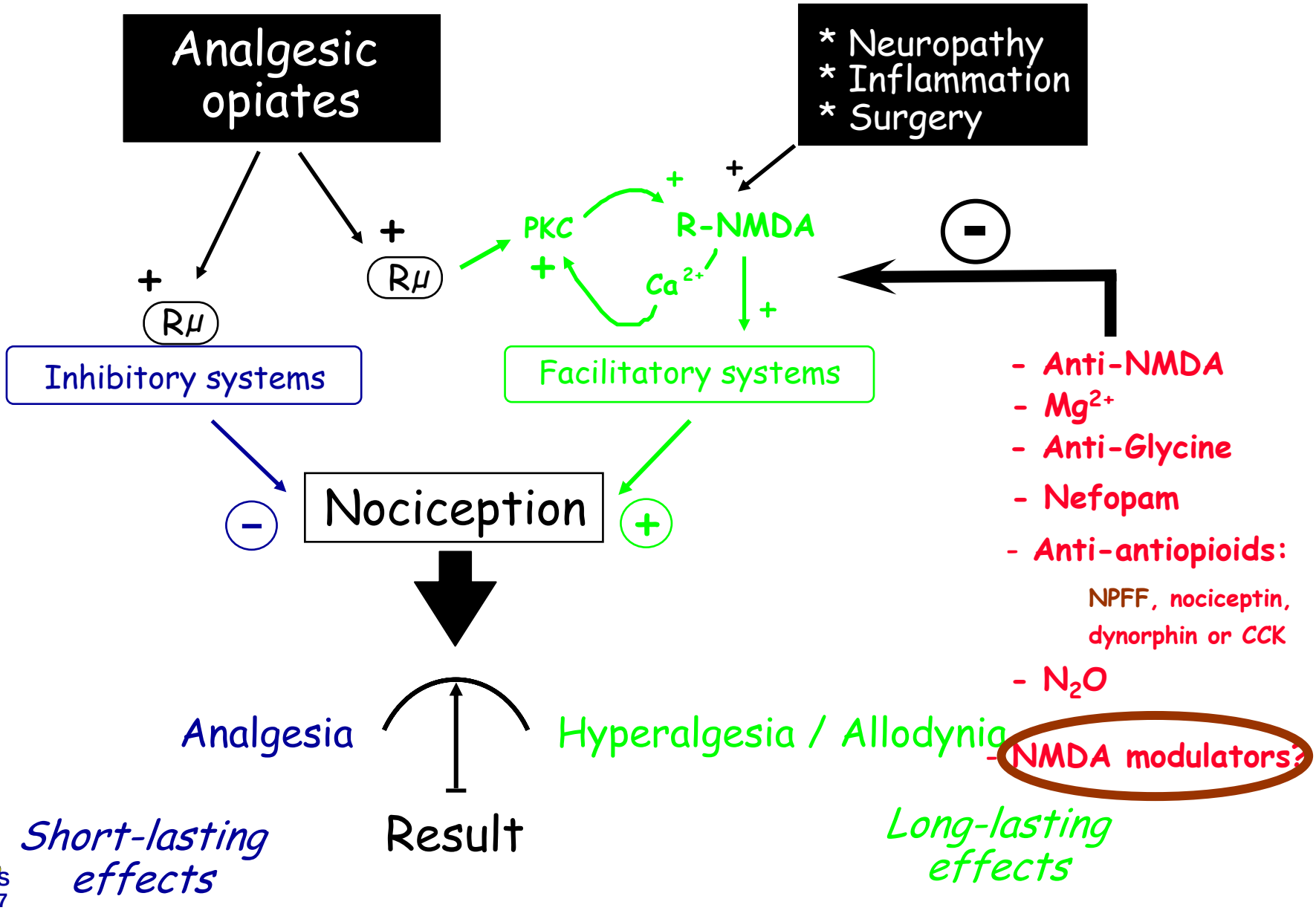
Un anti-hyperalgésique, non antinociceptif

Anesthesiology 2008; 108:484–94

Gabapentin Prevents Delayed and Long-lasting Hyperalgesia Induced by Fentanyl in Rats

Alain C. Van Elstraete, M.D., Philippe Sitbon, M.D.,† Jean-Xavier Mazoit, M.D., Ph.D.,† Dan Benhamou, M.D.‡*

Pharmacological proposals

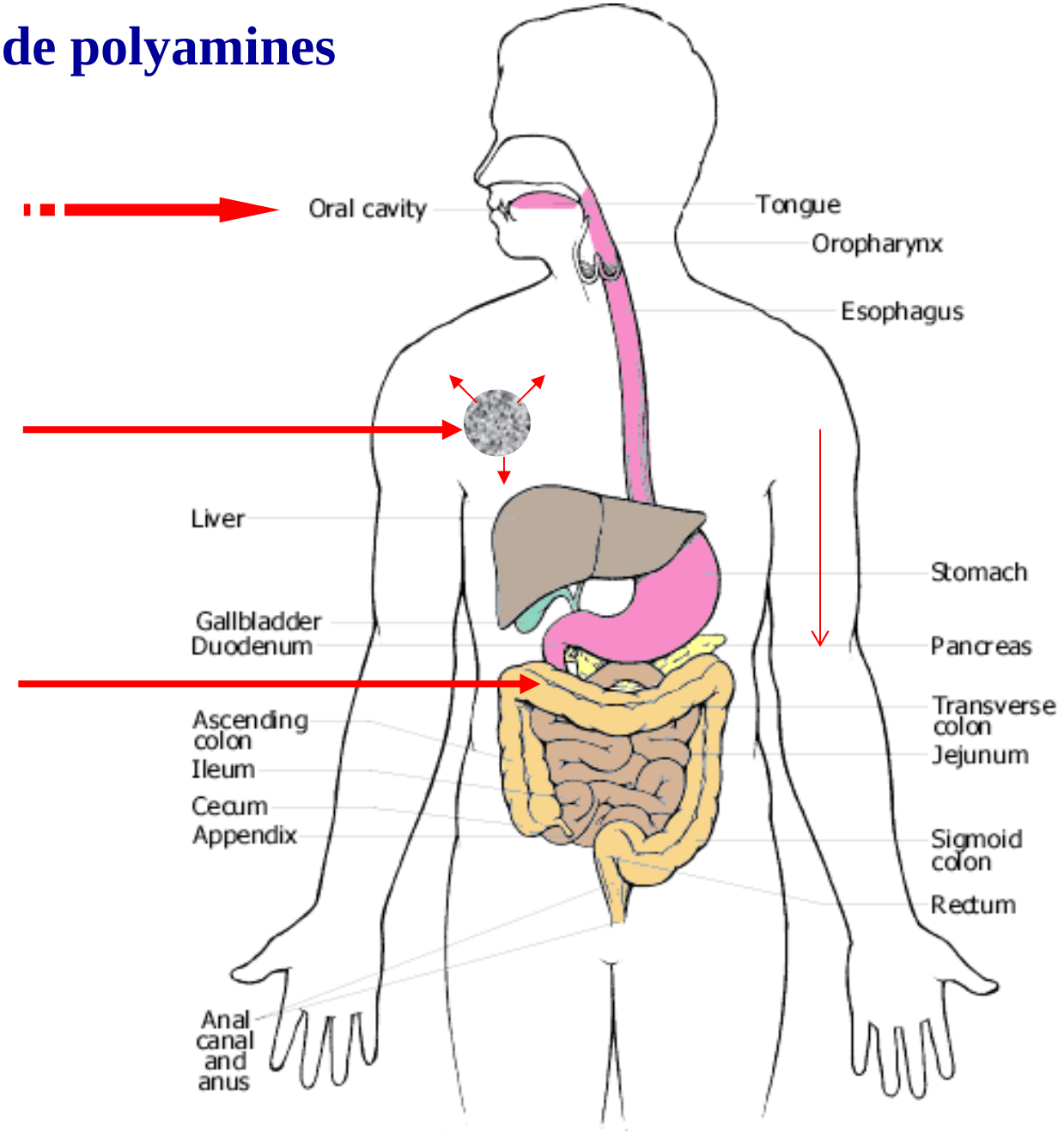


Sources principales de polyamines

Alimentation

Prolifération tumorale

Microflore intestinale

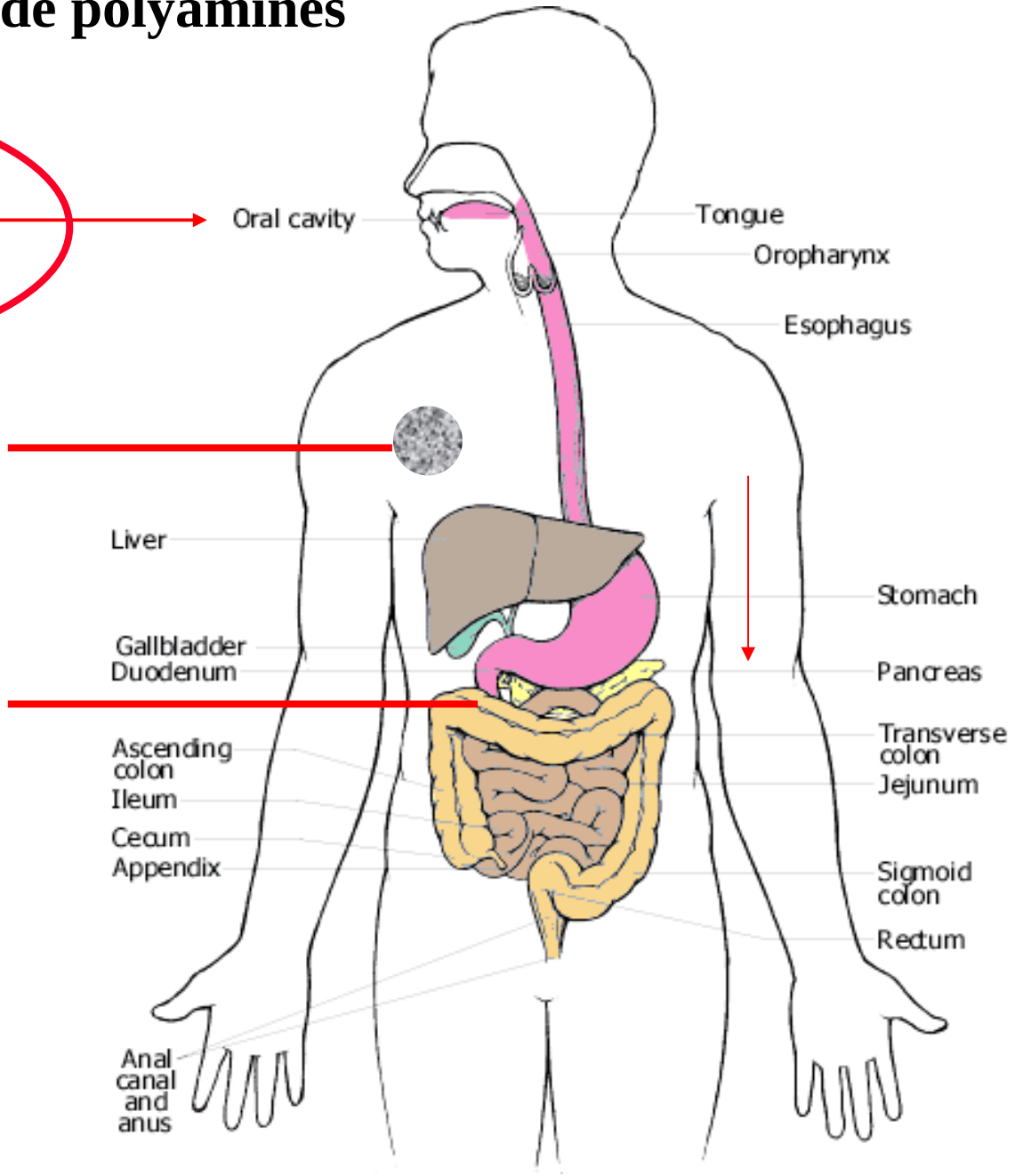


Réduction de 3 sources de polyamines

Alimentation
à faible teneur
en polyamines

Prolifération tumorale
DFMO *per os*

Microflore intestinale
néomycine

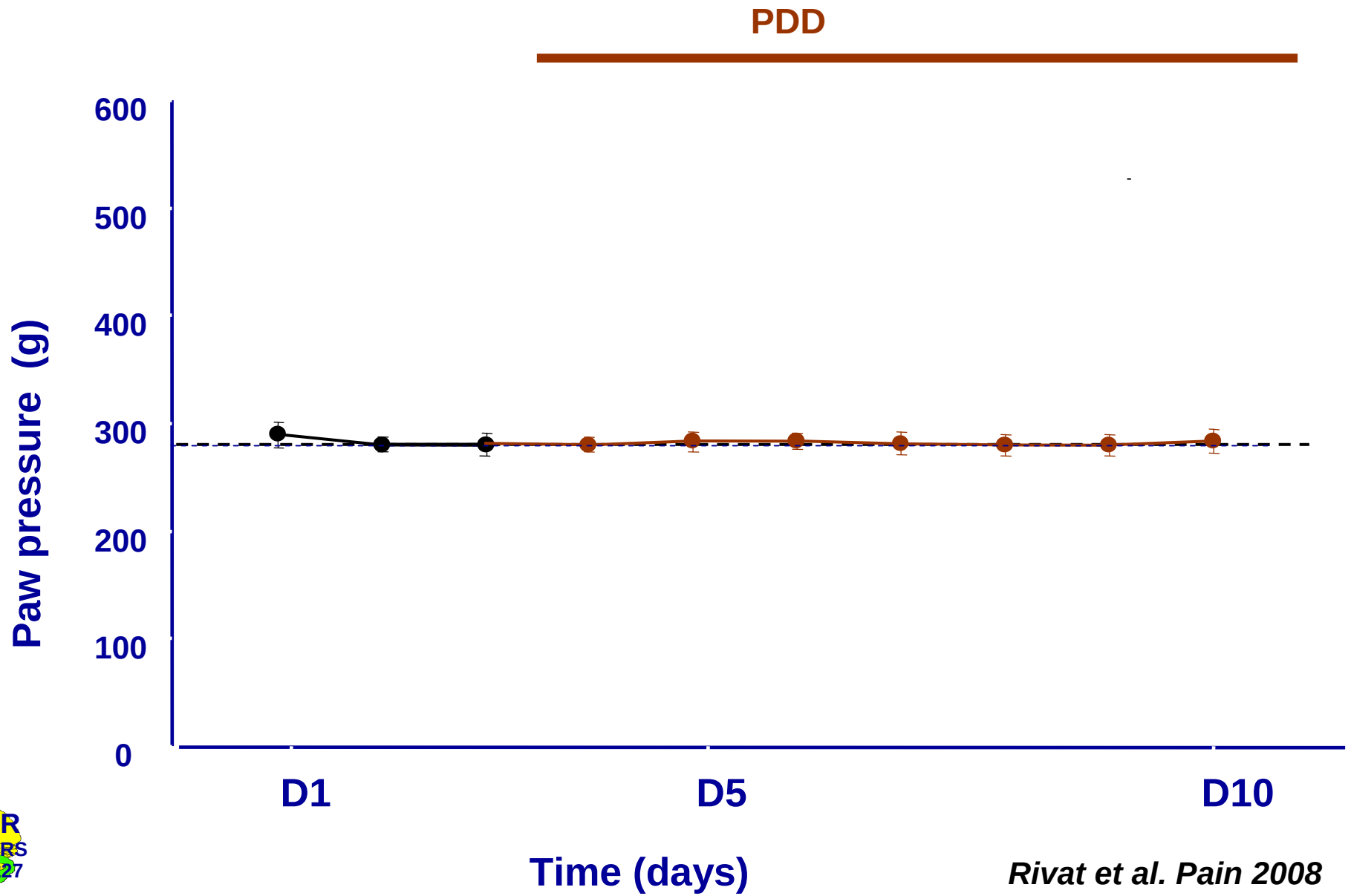


Dis-moi ce que tu manges,

et je te dirai…

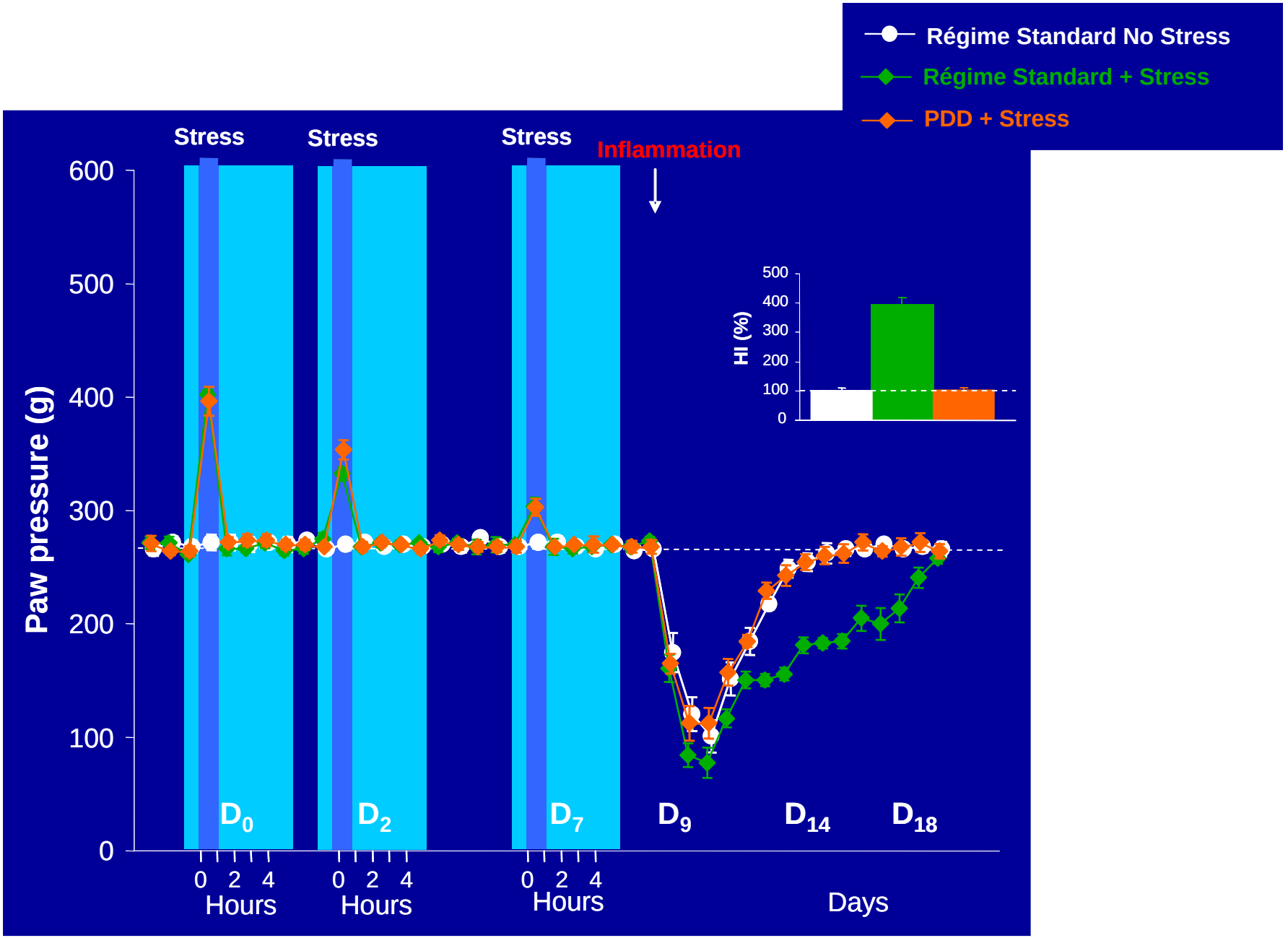
HAPR
Bx2-CNRS
UMR 5227

Effects of Polyamine deficient diet (PDD) on basal nociceptive threshold



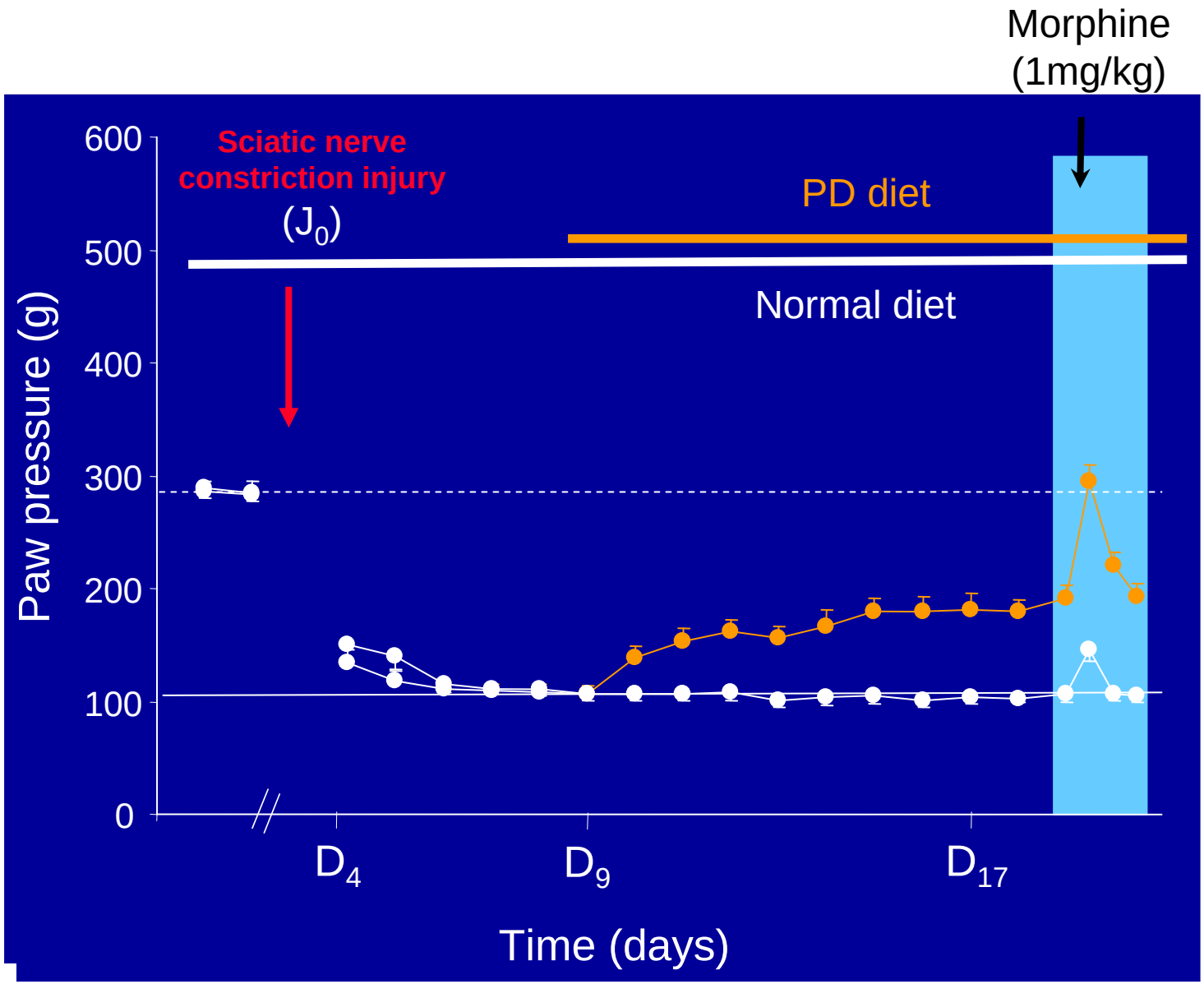
HAPR
Bx2-CNRS
UMR 5227

Rivat et al. Pain 2008



HAPR
Bx2-CNRS
UMR 5227

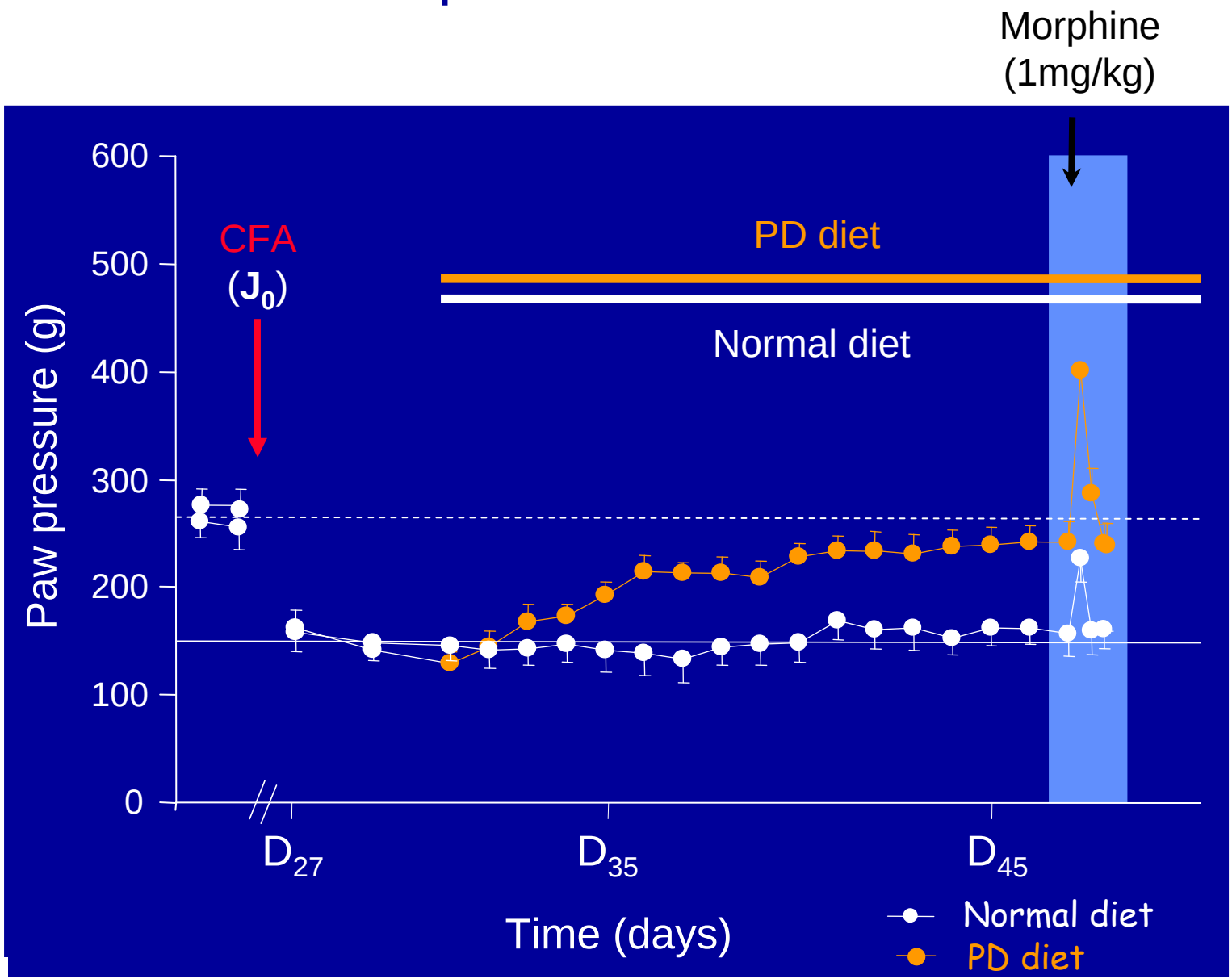
Relief of neuropathic pain



HAPR
Bx2-CNRS
UMR 5227

Rivat et al. Pain 2008

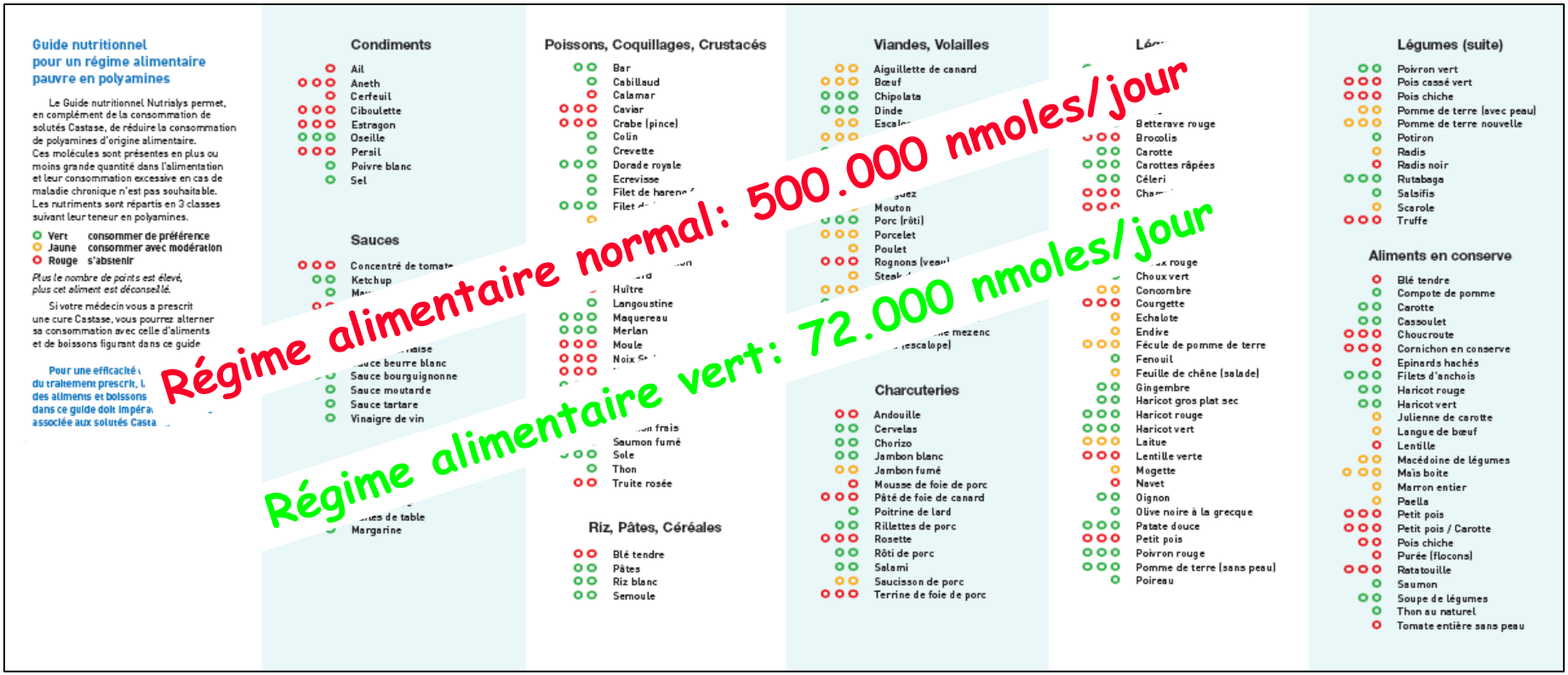
Osteo-monoarthtic pain model



Chez l'homme douloureux

ou…

avant une expérience douloureuse


Guide nutritionnel
pour un régime alimentaire
pauvre en polyamines
Le Guide nutritionnel Nutrialys permet, en complément de la consommation de solutés Castase, de réduire la consommation de polyamines d'origine alimentaire.
Ces molécules sont présentes en plus ou moins grande quantité dans l'alimentation et leur consommation excessive en cas de maladie chronique n'est pas souhaitable.
Les nutriments sont répartis en 3 classes suivant leur teneur en polyamines.
Vert consommer de préférence
Jaune consommer avec modération
Rouge s'abstenir
Plus le nombre de points est élevé, plus cet aliment est déconseillé.
Si votre médecin vous a prescrit une cure Castase, vous pourrez alterner sa consommation avec celle d'aliments et de boissons figurant dans ce guide
Pour une efficacité
du traitement prescrit,
des aliments et boissons
dans ce guide doit impéra
associée aux solutés Casta
Condiments
Ail
Aneth
Cerfeuil
Ciboulette
Estragon
Oseille
Persil
Poivre blanc
Sel
Sauces
Concentré de tomate
Ketchup
Sauce beurre blanc
Sauce bourguignonne
Sauce moutarde
Sauce tartare
Vinaigre de vin
Margarine
Poissons, Coquillages, Crustacés
Bar
Cabillaud
Calamar
Caviar
Crabe (pince)
Colin
Crevette
Dorade royale
Ecrevisse
Huître
Langoustine
Maquereau
Merlan
Moule
Saumon fumé
Sole
Thon
Truite rosée
Riz, Pâtes, Céréales
Blé tendre
Pâtes
Riz blanc
Semoule
Viandes, Volailles
Aiguillette de canard
Bœuf
Chipolata
Dinde
Mouton
Porc (rôti)
Porcelet
Poulet
Rognons (veau)
Charcuteries
Andouille
Cervelas
Chorizo
Jambon blanc
Jambon fumé
Mousse de foie de porc
Pâté de foie de canard
Poitrine de lard
Rillettes de porc
Rosette
Rôti de porc
Salami
Saucisson de porc
Terrine de foie de porc
Betterave rouge
Brocolis
Carotte
Carottes râpées
Céleri
Choux rouge
Choux vert
Concombre
Courgette
Echalote
Endive
Fécule de pomme de terre
Fenouil
Feuille de chêne (salade)
Gingembre
Haricot gros plat sec
Haricot rouge
Haricot vert
Laitue
Lentille verte
Mogette
Navet
Oignon
Olive noire à la grecque
Patate douce
Petit pois
Poivron rouge
Pomme de terre (sans peau)
Poireau
Légumes (suite)
Poivron vert
Pois cassé vert
Pois chiche
Pomme de terre (avec peau)
Pomme de terre nouvelle
Potiron
Radis
Radis noir
Rutabaga
Salsifis
Scarole
Truffe
Aliments en conserve
Blé tendre
Compote de pomme
Carotte
Cassoulet
Choucroute
Cornichon en conserve
Epinards hachés
Filets d'anchois
Haricot rouge
Haricot vert
Julienne de carotte
Langue de bœuf
Lentille
Macédoine de légumes
Maïs boîte
Marron entier
Paella
Petit pois
Petit pois / Carotte
Pois chiche
Purée (flocons)
Ratatouille
Saumon
Soupe de légumes
Thon au naturel
Tomate entière sans peau
Régime alimentaire normal: 500.000 nmoles/jour
Régime alimentaire vert: 72.000 nmoles/jour


polydol®
BOISSON AROME CHOCOLAT
BOISSON AROME CHO
Aliment Diététique Destiné à
Spéciales, pour les besoins
patients dénutris présentant ou
chroniques, sous forme buvable.
• à faible teneur en polyamines.
• hypercalorique, hyperprotéique.
• riche en acides gras oméga 3.
• sans gluten, sans lactose.
CONDITIONS D'UTILISATION
Selon prescription médicale
et dans le cadre d'une alimentation
en polyamines*.
Bien agiter avant emploi, puis
secondes avant ouverture et consom
Polydol chocolat peut se boire
ambiante ou tiède (dans un réci
secondes environ au micro-ondes
AVIS IMPORTANT
ouverture, puis 24 heures maximum
(4°C) après ouverture.
NUTRIALYS Medical Nu
Parc Edonia - Rue de la Terre
35760 Saint Grégoire
www.nutrialys.fr
ons complémentaires
au 0811 46 28 56
(coût d'un appel local)
80 à 120 nmoles/jour
(0.02%)
NUTRIALYS
MEDICAL NUTRITION

Conclusion

- Tous ces travaux sont en faveur d'une nouvelle classification des antalgiques différente de celle de l'OMS

- La formation des thérapeutes est loin d'être ouverte au concept :
  - Antalgie / hyperalgie
  - Antinociceptif / non antinociceptif