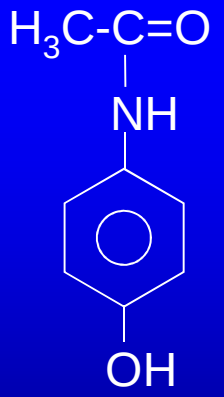
Inserm

UMR 766

UNIVERSITE D'AUVERGNE
CLERMONT-FD1



Paracetamol
***N*-acetyl-*p*-aminophenol**

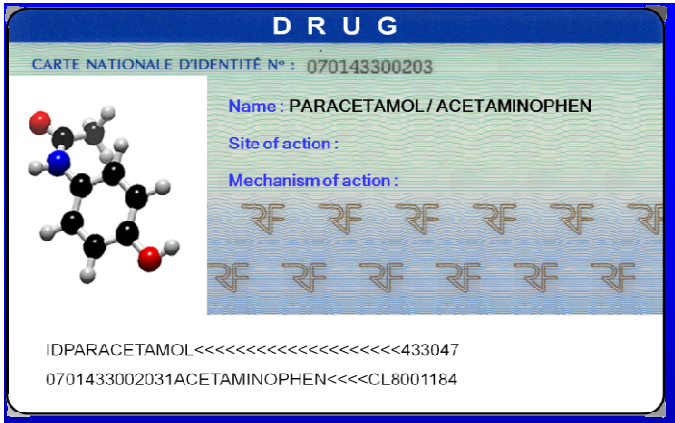
Action antalgique du paracétamol: un mécanisme complexe et surprenant

CHU CLERMONT FERRAND

SERVICE DE PHARMACOLOGIE

A. ESCHALIER

16 09 2010



UN AMI DE PLUS DE 30 ANS, FIDELE ET SANS SURPRISE!...

* ANALGESIQUE PERIPHERIQUE

* EFFICACITE ANALGESIQUE MODEREE DANS LES DOULEURS AIGUES.

* MEDICAMENT BIEN TOLERE.

* UTILISE EN AUTOMEDICATION.

* REFERENCE CHEZ L'ENFANT ET LA FEMME ENCEINTE.

* EFFICACITE ACCRUE SI ASSOCIATION AVEC OPIOIDES

* RISQUE DE TOXICITE HEPATIQUE EN SURDOSAGE.

UN AMI MYSTERIEUX

1877 : synthèse par Morse
1887 : première utilisation clinique (Von Mehring)

ABANDON

1955 : AMM aux USA

Aujourd'hui: l'antalgique le plus utilisé au monde

UN MYSTERE PERSISTE:
SON MECANISME D'ACTION?

MAIS POURQUOI S'INTERESSER A SON MECANISME D'ACTION?

BESOIN D'INNOVATION EN ANTALGIE

Morphine (1803)
Aspirin (1899)
Paracetamol (1877)
AINS (1953)
Ibuprofen (1961)
Antidepressants (1960)
Antiepileptics (1958)

BESOIN D'INNOVATION EN ANTALGIE

PAS DE PROGRES CONCEPTUEL EN PHARMACOLOGIE DE LA DOULEUR

DES ANTALGIQUES AVEC UN RATIO BENEFICE-RISQUE INSATISFAISANT

DES SYNDROMES DOULOUREUX MAL PRIS EN CHARGE

UN PARADOXE

UNE VARIETE ETIOLOGIQUE

UNE DIVERSITE PHYSIOPATHOLOGIQUE

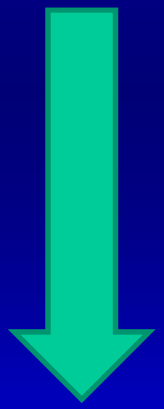
DES CONCEPTS PHARMACOLOGIQUES LIMITES
UNE GRANDE PLACE A L'EMPIRISME

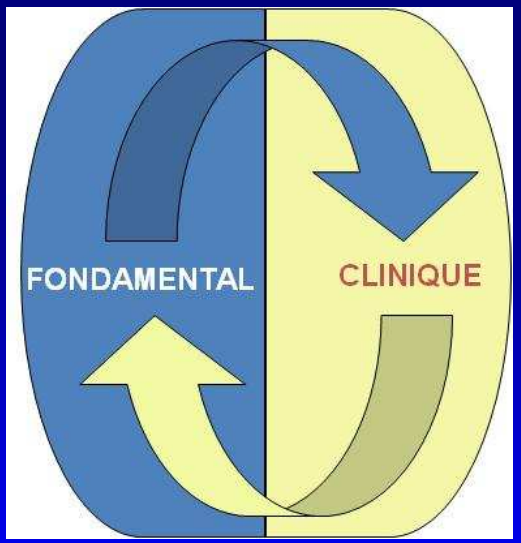
UN BESOIN D'INNOVATION THERAPEUTIQUE FORT

MAIS POURQUOI S'INTERESSER A SON MECANISME D'ACTION?

Analyse des
mécanismes d'action ou
d'effets indésirables d'antalgiques

Comportement
Biochimie
Génomique fonctionnelle
In vitro
Essais cliniques





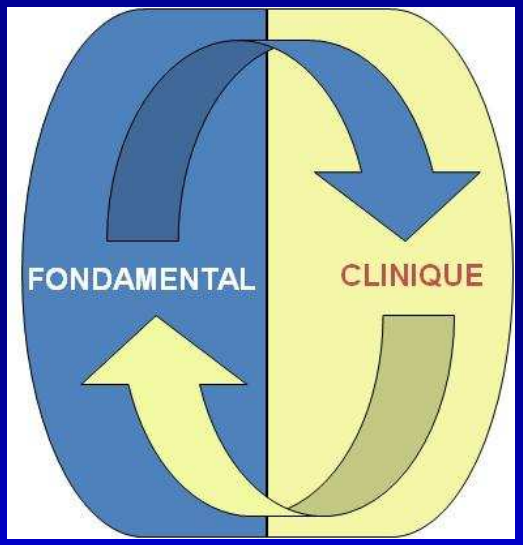
IDENTIFICATION DE
NOUVELLES CIBLES

PERTINENCE CLINIQUE

QUELLE STRATEGIE POUR INNOVER?

Analyse de
mécanismes d'action ou
d'effets indésirables d'antalgiques

Analyse
du rôle physiopathologique
de protéines d'intérêt



IDENTIFICATION DE NOUVELLES CIBLES

Analgesia Partnership

PHARMACOLOGIE

CLINIQUE

HYPOTHESE

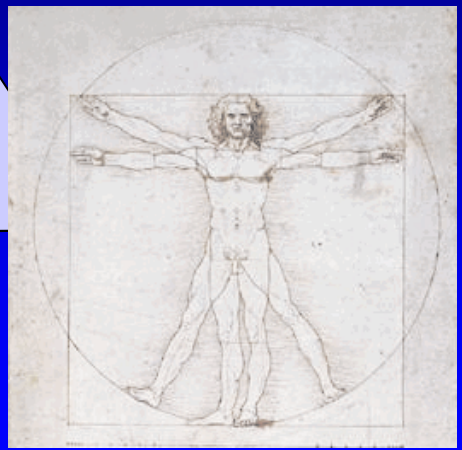
IN VITRO

VERIFICATION
ANALYSE

CONCEPT

EX VIVO

PREUVE DE CONCEPT



VALIDATION CLINIQUE

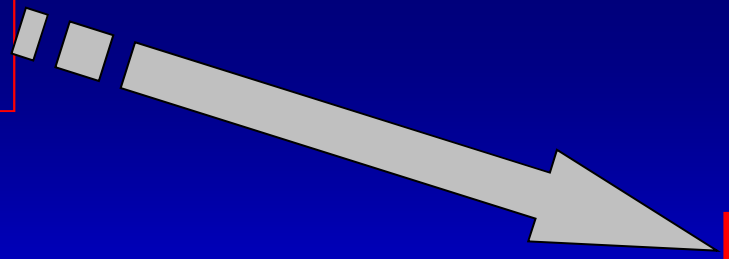
UN PROFIL CLINIQUE PARTICULIER

	AINS	PARACETAMOL
EFFETS BENEFIQUES		
Analgésique	+	+
Antipyrétique	+	+
Anti-inflammatoire	+	?
Anti-agrégant	+	-
EFFETS INDESIRABLES		
Toxicité gastrique	+	-
Hémorragie	+	-
Troubles obstétricaux	+	-
Insuffisance rénale aiguë	+	-
Hypersensibilité	+	+/-

A LA LUMIERE DE LA CLINIQUE

UNE REMISE EN CAUSE DES DONNES CLASSIQUES

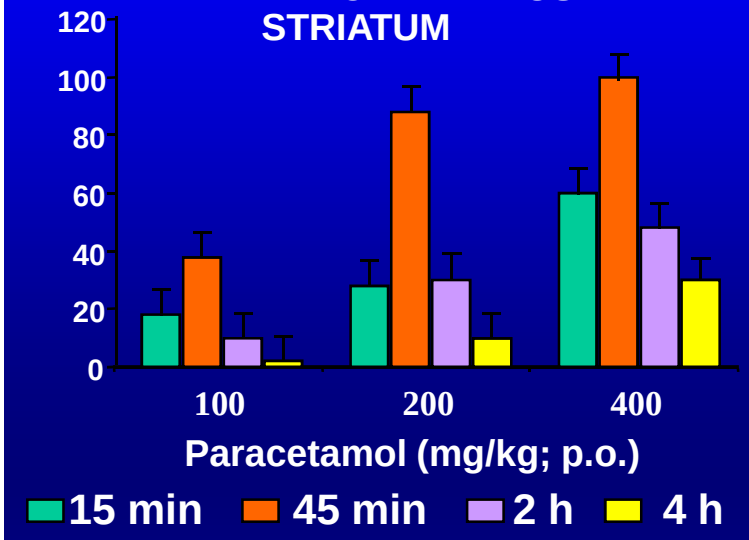
UN « NSAID-like drug »

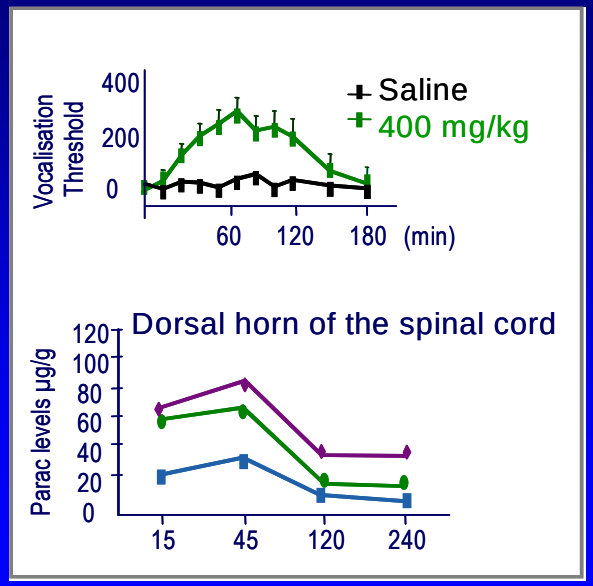


UN ANTALGIQUE CENTRAL

PREUVES PHARMACOCINETIQUES POUR UN EFFET CENTRAL

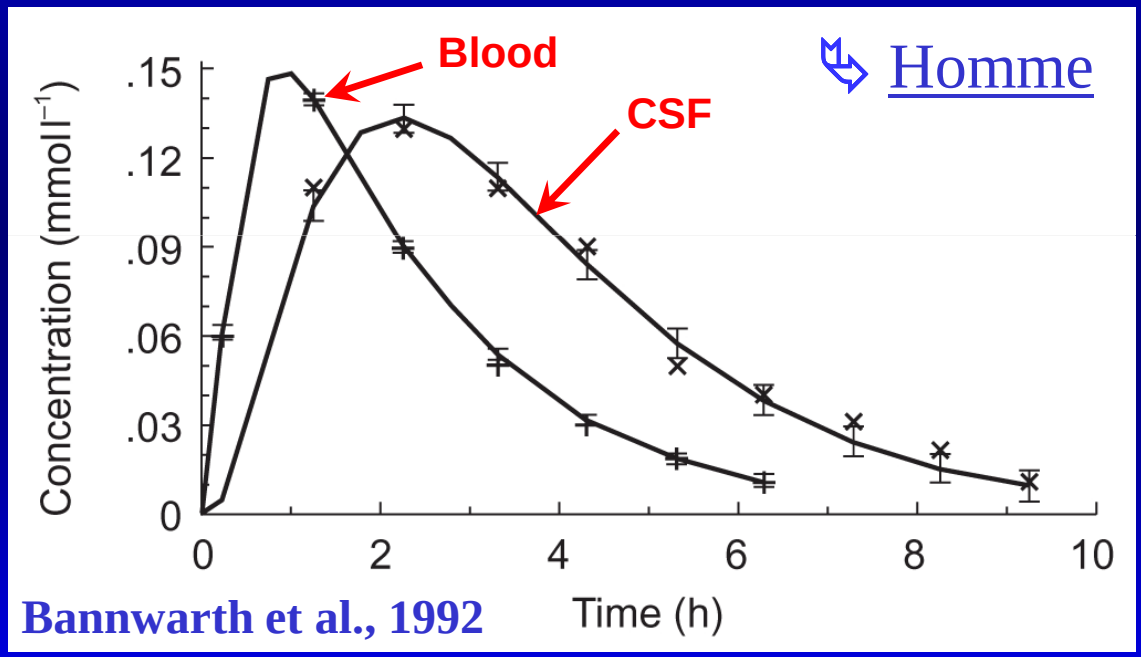
Rats





Courade et al., 2001

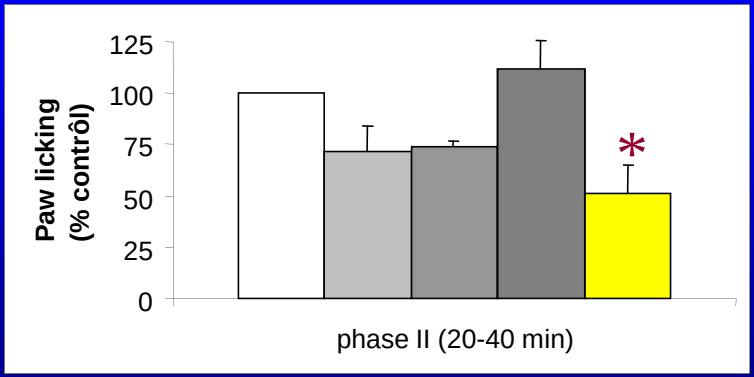
Homme



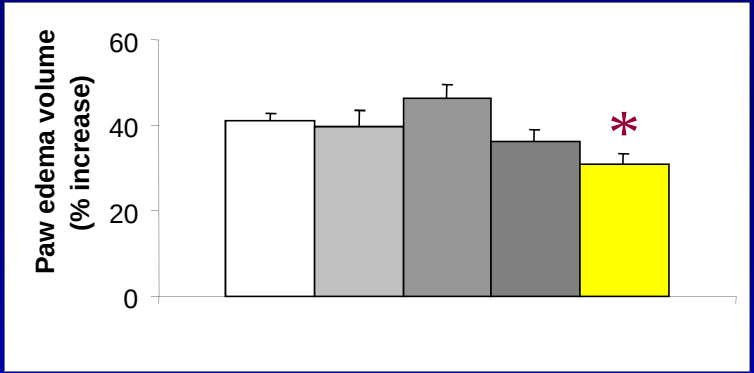
Bannwarth et al., 1992

PREUVES PHARMACODYNAMIQUES

ABSENCE D'EFFET PERIPHERIQUE CHEZ LE RAT



Bonnefont et al., 2003



NaCl 0,9 % (i.pl.)

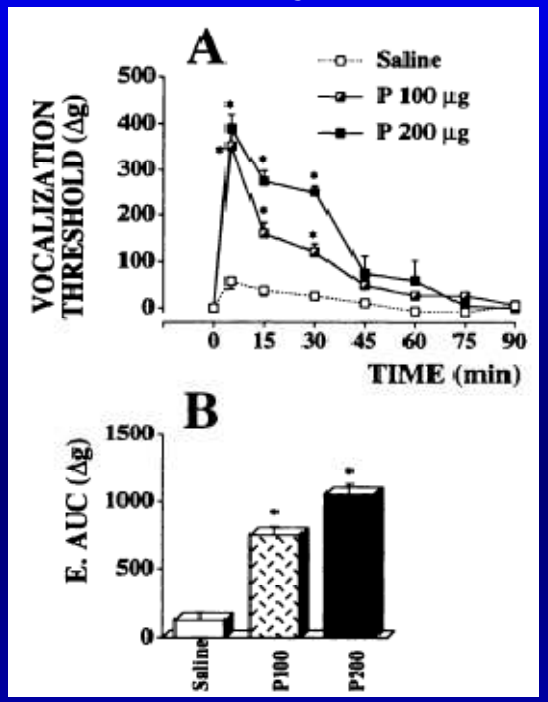
Paracetamol 0,1 mg/kg

Paracetamol 1 mg/kg

Paracetamol 10 mg/kg

Indomethacine 1,8 mg/kg

i.t. injection



Pélissier et al., 1996

EFFICACE DANS DES TESTS DE DOULEUR NON-INFLAMATOIRE CHEZ L'HOMME

RIII FLEXOR REFLEX: Piletta et al., 1991 **PAINFUL LASER STIMULATION:** Nielsen et al., 1991, 1992

INTRACUTANEOUS ELECTRICAL PULSES: Bromm et al., 1992 **COLD-INDUCED PAIN:** Yuan et al., 1998

PAIN MATCHER: Pickering et al., 2006; 2008

nature REVIEWS NEUROSCIENCE

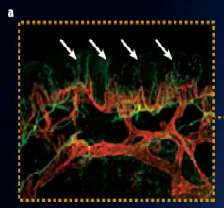
Pain mechanisms

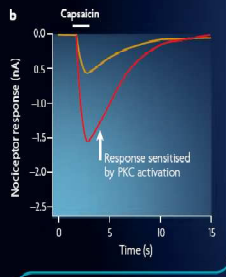
Stephen McMahon and David Bennett

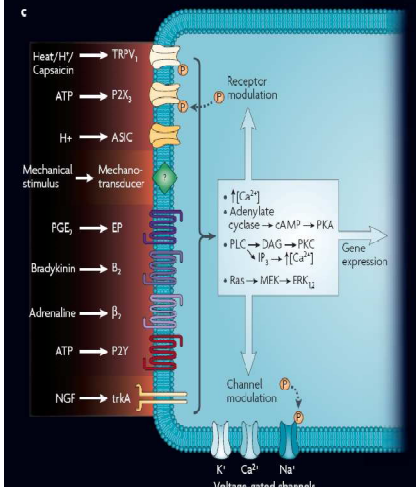
Pain is an unpleasant sensation resulting from the intricate interplay between sensory and cognitive mechanisms. Chronic pain, resulting from disease or injury, affects nearly every fifth person in the Western world, constituting an enormous burden for the individual and society. Sensitization of pain signalling systems is a key feature of chronic pain and results in normally non-painful stimuli eliciting pain. Such sensory changes can occur not just at the sites of injury, but in surrounding normal tissues. This and other observations suggest that sensitization occurs within the CNS as well as within nociceptor terminals. Here we have taken the approach of considering the consequences of a noxious stimulus applied to our unfortunate builder's hand, from sensory transduction to pain perception. We describe the structural and functional elements present at different levels of the nociceptive system, as well as some of the changes occurring in chronic pain states. Although our poster highlights a flow of information from the periphery to the central nervous system, it should be noted that higher brain centres exert both inhibitory and facilitatory controls on lower ones. The challenge for the next decade will be to effectively translate this knowledge into the development of novel analgesic agents for better pain relief.

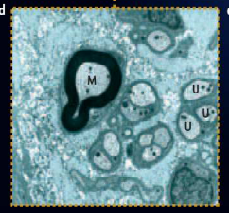
Peripheral nociceptor terminals

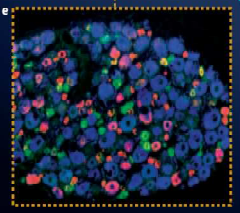
Nociceptors are essential for the appreciation of pain. These primary sensory neurons have cell bodies in the dorsal root or trigeminal ganglia, and possess naked peripheral endings that terminate within the epidermis (arrows, **a**). Ion channels in the plasma membrane of nociceptors have a key role in the transduction of stimuli such as heat or pain-producing chemicals, as illustrated in **c**. The ion channel(s) that responds to noxious mechanical stimuli is still unknown. Inflammation will result in the production of a large number of mediators (for example, prostaglandin, bradykinin and nerve growth factor (NGF)). These mediators bind to G-protein-coupled or, in the case of NGF, tyrosine kinase, receptors on the nociceptor terminal, resulting in the activation of multiple second messenger pathways that have an important role in sensitization. Sensitization is achieved by receptor and/or channel modulation and — over a longer period of time — by alterations in gene expression. One example of such sensitization is shown in **b**, where the activation of protein kinase C facilitates the response of sensory neurons to capsaicin.

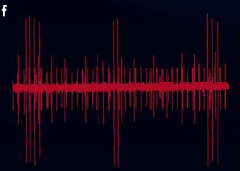






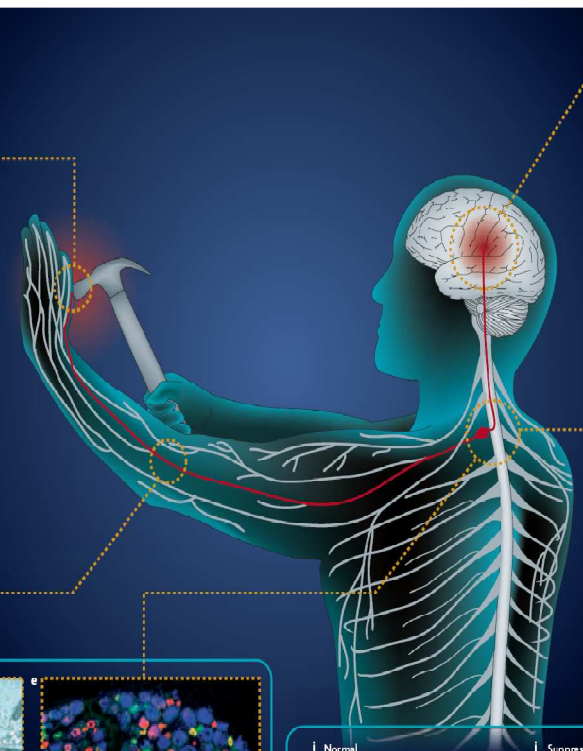


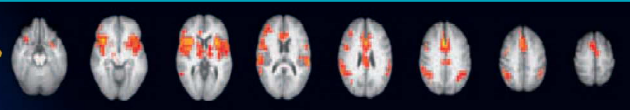




Peripheral nerves and the DRG

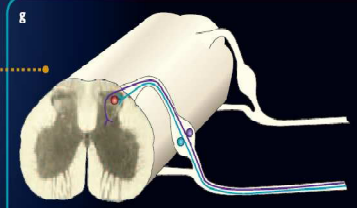
In peripheral nerves, nociceptors have unmyelinated or thinly myelinated axons (**d** is an electron micrograph of a cross-section of a human nerve, showing one large myelinated (M) and multiple unmyelinated (U) fibres). Nociceptors have a lower conduction velocity compared with other peripheral sensory nerve fibres. Within the dorsal root ganglion (DRG), nociceptive afferents mostly have small diameter cell bodies and can be identified by particular patterns of gene expression. They can be divided into those that express neuropeptides (red in **e**) and those that are non-peptidergic (green in **e**). Large diameter, mostly non-nociceptive afferents are shown in blue. The development of ectopic (spontaneous) activity in primary afferents following nerve injury (**f**) is likely to contribute to the generation of neuropathic pain. In addition, injured axons develop a novel mechanosensitivity and an increased response to catecholamines, changes that are likely to represent alterations in ion channel expression and trafficking within DRG cells.

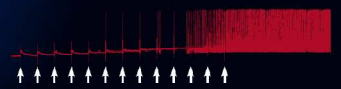




Brain

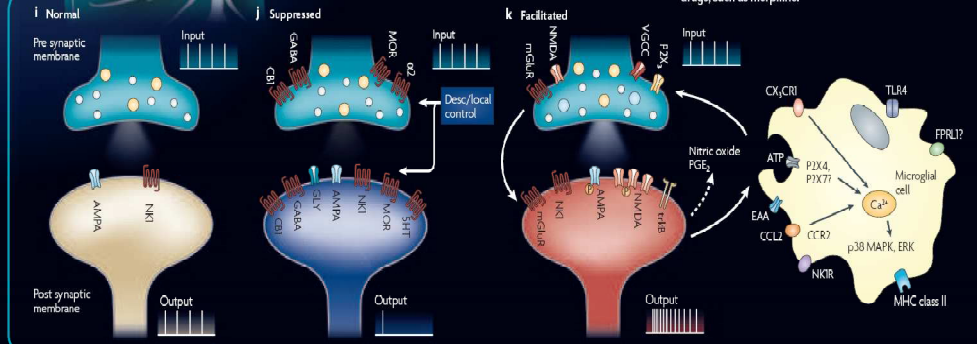
Neuroimaging with functional MRI allows direct evaluation of where pain is represented in the brain. A painful stimulus reliably leads to activation of multiple brain areas, commonly referred to as the pain matrix. Figure **l** shows an example of activation of this matrix in one individual in a series of axial brain sections after the application of noxious heat to one hand. The strength of activation is colour-coded (red indicating moderate, yellow for strong responses). The different areas activated are thought to be associated with different aspects of pain. S1 and S2 (the primary and secondary somatosensory cortices, respectively) may primarily function to discriminate the location and intensity of a painful stimulus, while the anterior cingulate cortex, frontal cortex and anterior insula regions seem to be more involved in cognitive and emotional components. Other areas less commonly activated, including the amygdala and the entorhinal complex, are associated with fear and anxiety. The different brain areas also show strong modulation depending on the context in which the stimulus is given, including the degree of attention/distraction, anxiety, expectation, depression and following analgesic drug treatment.



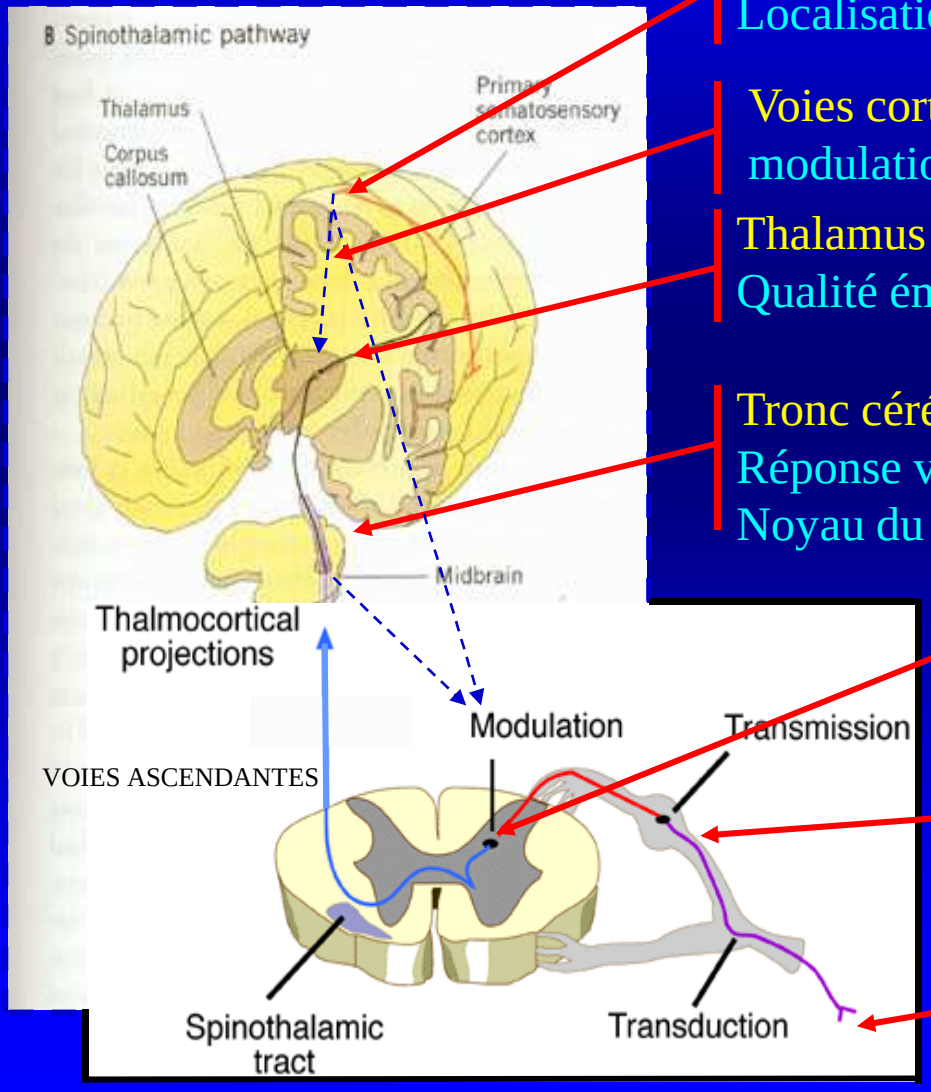


Spinal cord

Primary afferent nociceptors mostly terminate in the spinal cord (**g**), which has an important role in the integration and modulation of pain-related signals. Second-order neurons receiving input from nociceptors and projecting to the brain are located in both superficial and deep laminae of the dorsal horn. These cells often have convergent inputs from different sensory fibre types and even different tissues. Spinal nociceptive processing exhibits activity-dependent plasticity (**i–k**), as repetitive activity can induce long-lasting facilitation in output systems (**h**). Such enhanced responses, generically referred to as central sensitization, add to the abnormal pain sensitivity seen in many chronic pain states. Multiple processes seem to contribute to these states, including the enhancement of presynaptic transmitter release and, crucially, recruitment of postsynaptic NMDA (*N*-methyl-D-aspartate) receptors (**k**). Non-neuronal cells, particularly microglia, release mediators that are a factor in central sensitization. Both pre- and postsynaptic elements are strongly gated by descending facilitatory and inhibitory influences from the brain. The inhibitory influences (**j**) use neurotransmitters that are mimicked by some analgesic drugs, such as morphine.



PHYSIOLOGIE DE LA NOCICEPTION



Cortex somatosensoriel (SI)…
Localisation & prise de conscience

Voies corticofuges
modulation de l'information

Thalamus
Qualité émotionnelle & Importance

Tronc cérébral
Réponse végétative & Inhibition descendante
Noyau du Trijumeau

Neurones de la corne dorsale
Modulation & Réponse réflexe

Fibres C et Aδ périphériques:
Transmission du signal

Nocicepteurs:
Captent la douleur

MECANISME D' ACTION

- Inhibition des COX

- Mécanisme sérotoninergique

- Mécanisme cannabinoïde

- Implication de TRPV1.....

INHIBITION DES COX: LA 1ère HYPOTHESE


Flower and Vane, 1972

In vitro experiments

	ID50 µg/ml		
	Dog spleen	Rabbit brain	Dog brain
Indomethacin	0.06	1.3	
Sodium aspirin	6.6	11.0	
4 - Acetamidophenol	100.0	14.0	12.5

In peripheral cells

* many discrepancies but, at best, paracetamol is a weak inhibitor
* peroxides reduce inhibitory effect of paracetamol on COX

In vivo experiments

* Paracetamol reduces spinal PG release, there are discrepancies

WHAT KIND OF COX ISOFORM ?

COX-3, a cyclooxygenase-1 variant inhibited by acetaminophen and other analgesic/antipyretic drugs: Cloning, structure, and expression

N.V. Chandrasekharan, Hu Dai, K. Lamar Turepu Roos, Nathan K.Evanson, Joshua Tomsik, Terry S. Elton, and Daniel L.Simmons*

Department of Chemistry and Biochemistry, E280 Benson Science Building, Bringham Young University, Provo, UT 84602

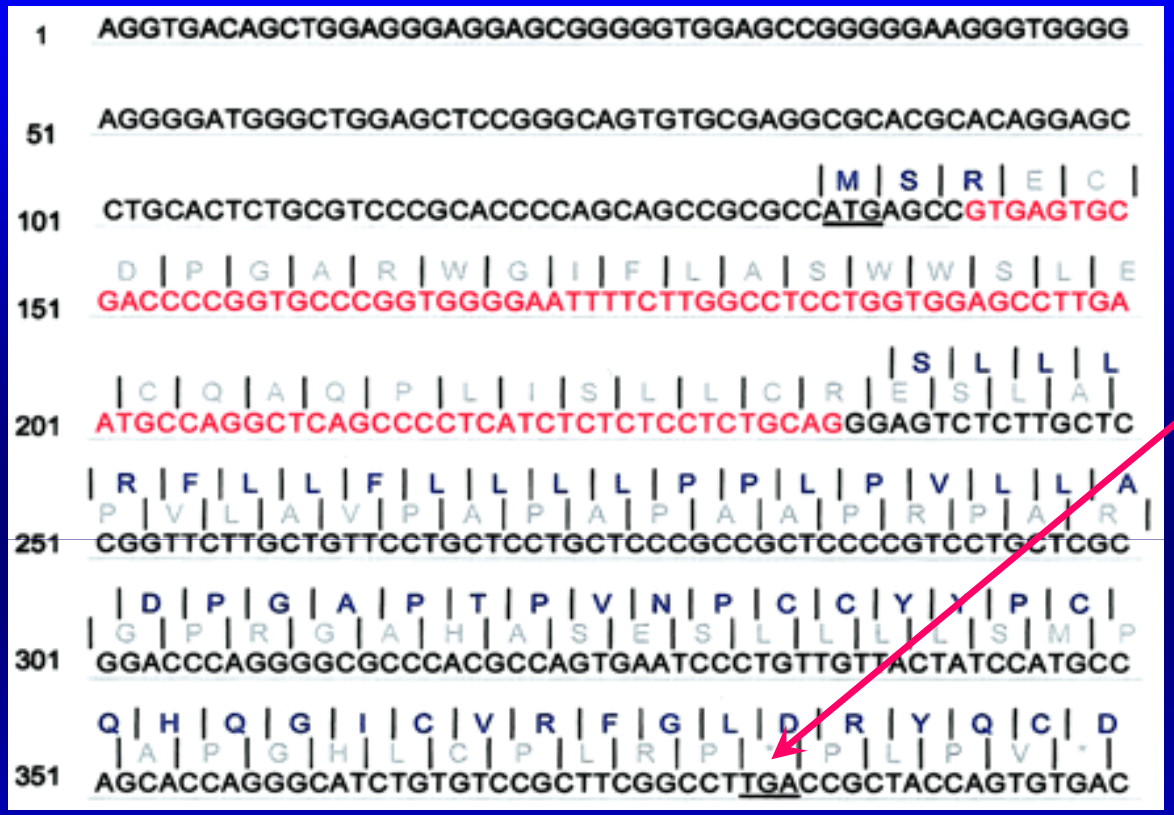
Communicated by John Vane, William Harvey Foundation, London, United Kingdom, August 5,2002 (received for review April 17, 2002)

Sf9 cells

	COX1	COX2	COX3
Indomethacin	0.01	0.66	0.016
Aspirin	10	>1,000	3.1
Diclofenac	0.035	0.041	0.008
Ibuprofen	2.4	5.7	0.24
Naproxen	/	/	/
Dipyrone	350	>1,000	52
Phenacetin	>1,000	>1,000	102
Paracetamol	>1,000	>1,000	460

Chandrasekharan et al 2002

Controverse à propos de la COX-3 !

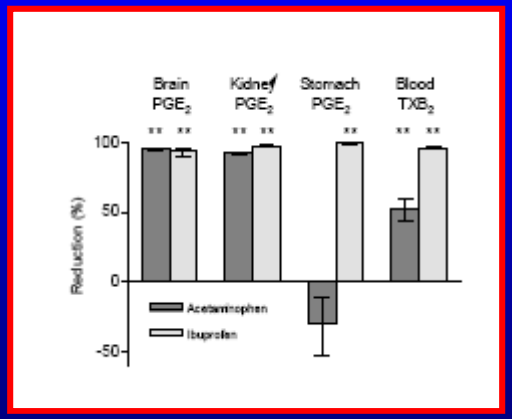


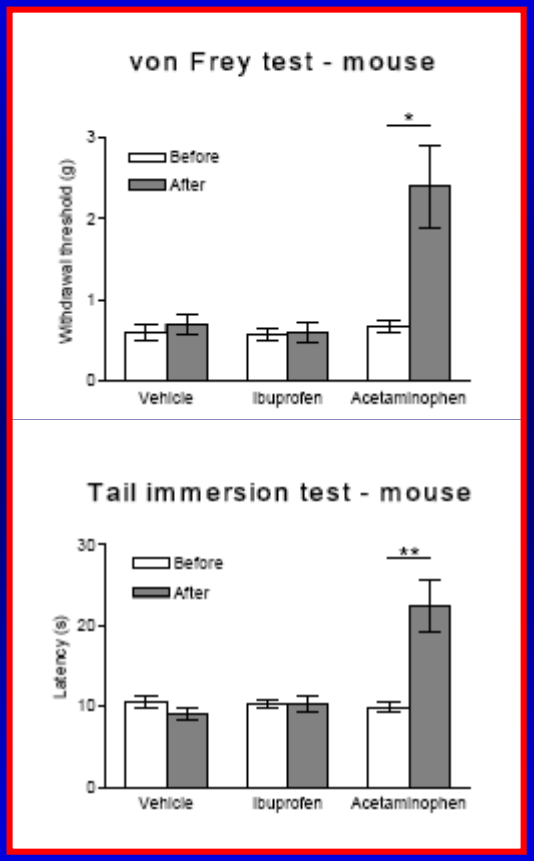
Le mRNA de la COX-3 code une protéine différente des COX.
Cox-3 existe dans différents tissus mais n'a pas d'activité COX

Snipes et al., 2005

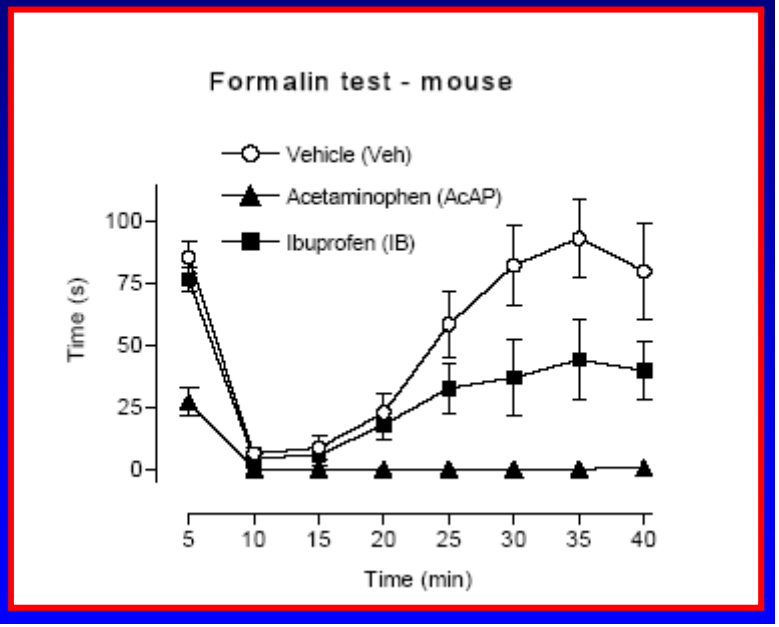
Kis et al., 2006

PAS D'IMPLICATION DES PGS DANS L'EFFET DU PARACETAMOL





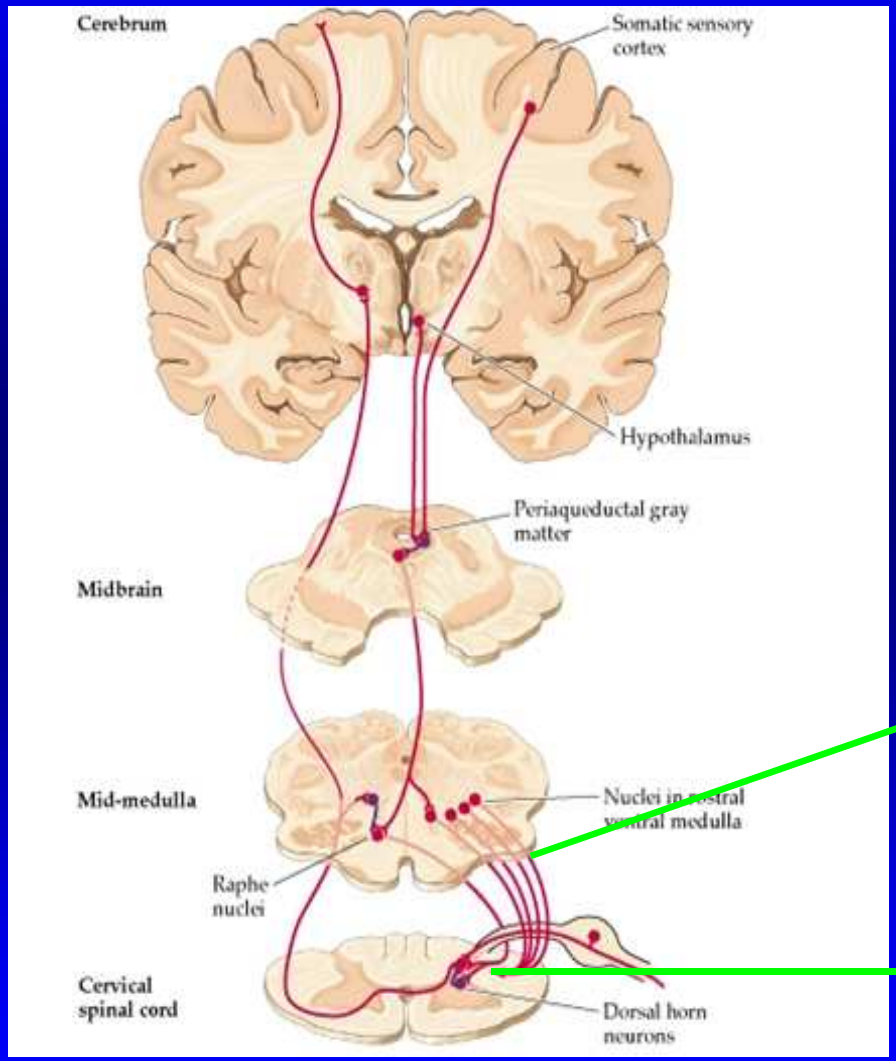
Paracétamol 200 mg/kg:
Ne réduit pas les taux de PGs
Est antalgique



Paracétamol, 300mg/kg

Mallet et al, PLoS ONE, 2010

PREUVES D'UN MECANISME SEROTONINERGIQUE CENTRAL



Tjolsen et al., 1991
Pini et al., 1996
Pélissier et al., 1996
Srikiatkhachorn et al., 1999
Courade et al., 2001
Alloui et al., 2002
Chen & Bazan, 2003
Libert et al., 2004
Pickering et al. 2006
Pickering et al. 2008

Effet antinociceptif inhibé par *p*CPA

Effet antinociceptif inhibé par 5,6-DHT (i.t.)

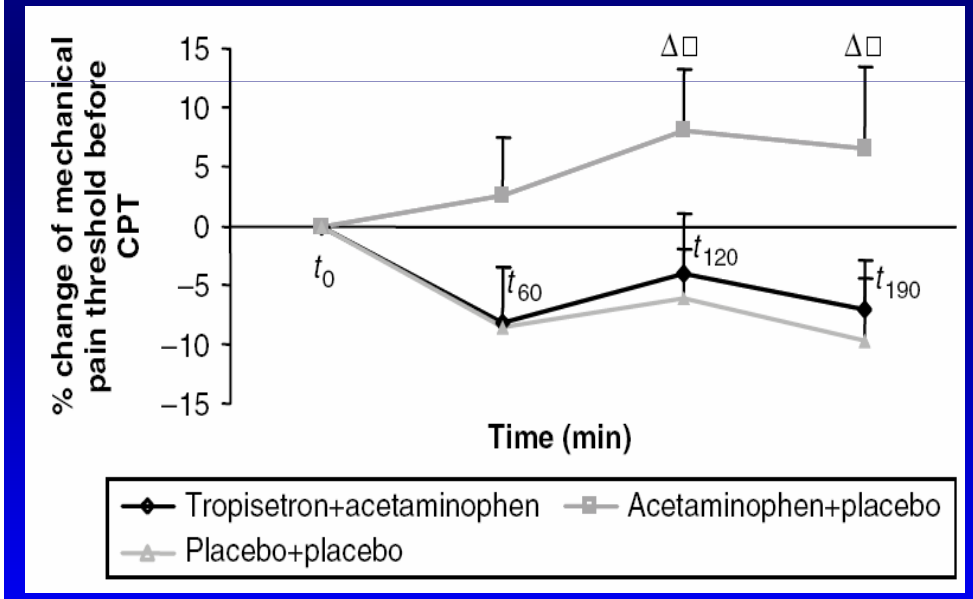
Effet antinociceptif inhibé par antagonistes 5-HT $_{1B, 2A, 2C, 3}$

Acetaminophen Reinforces Descending Inhibitory Pain Pathways

G Pickering[1,2,3], V Estève[1], M-A Loriot[4,5], A Eschalier[2,3,6] and C Dubray[1,2,3]

Pickering et al., Clin Pharmacol Ther. 2008

CPT= Cold Pressure Test



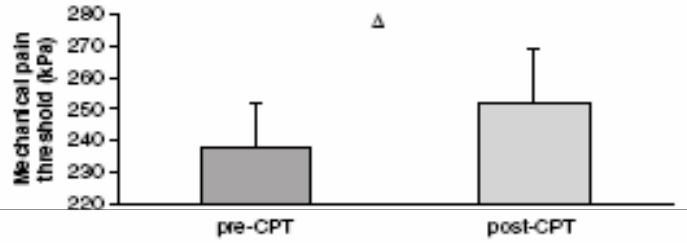


Figure 2 The CPT increases mechanical pain thresholds by stimulation of descending inhibitory pathways (Δ: $P<0.05$).

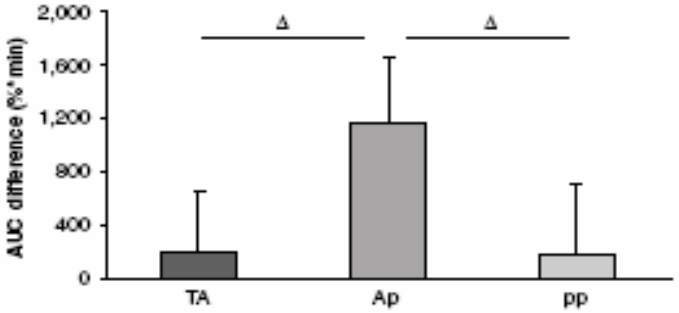
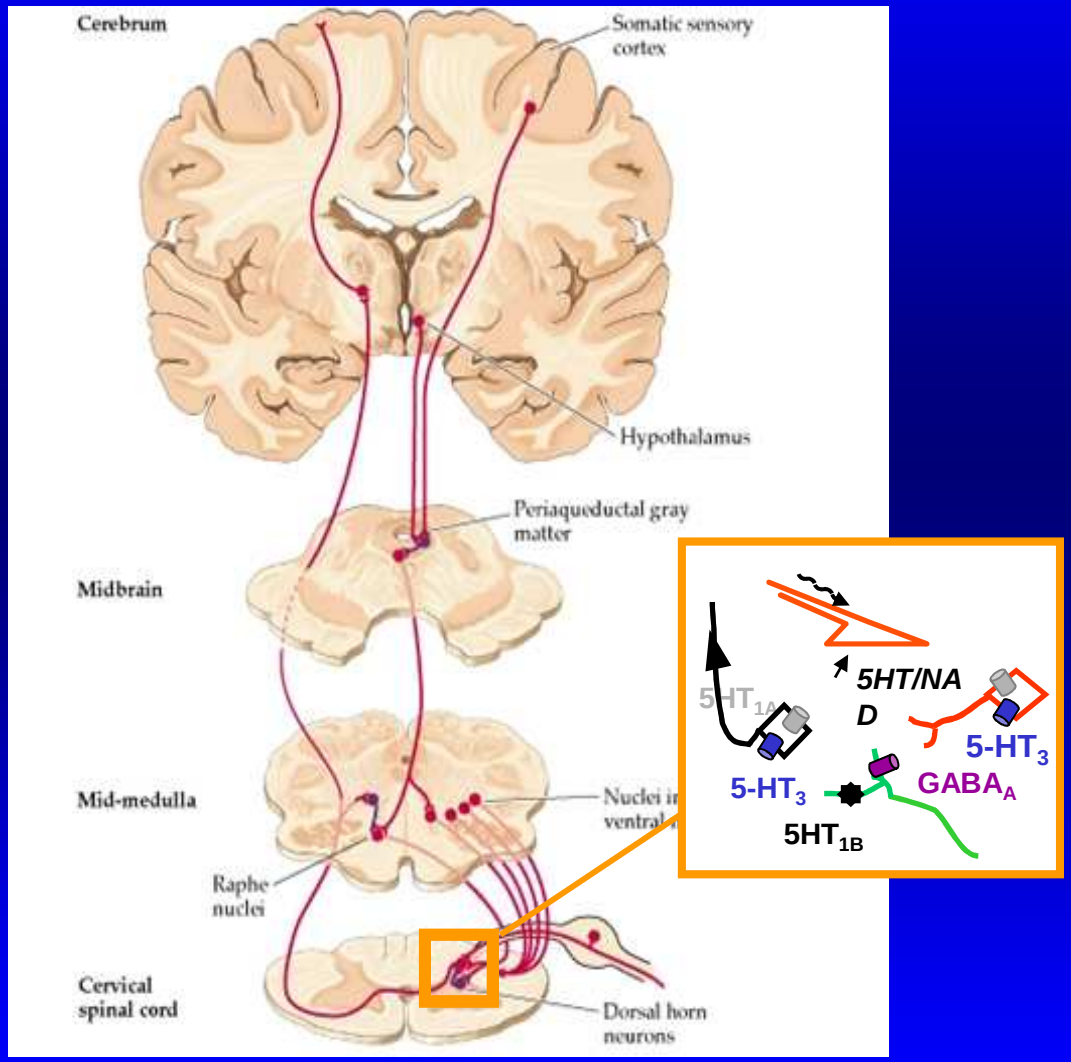
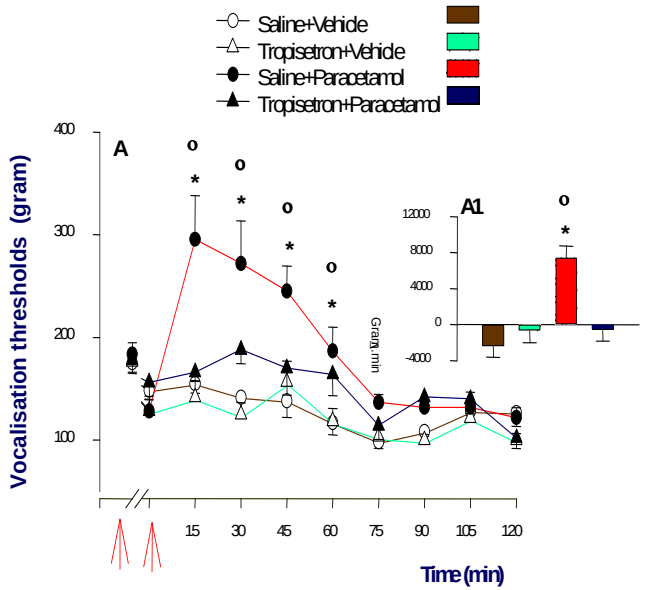


Figure 3 AUC differences between post- and pre-CPT sessions for the three treatments (Δ: $P<0.05$).

MECANISME SEROTONINERGIQUE CENTRAL RAT

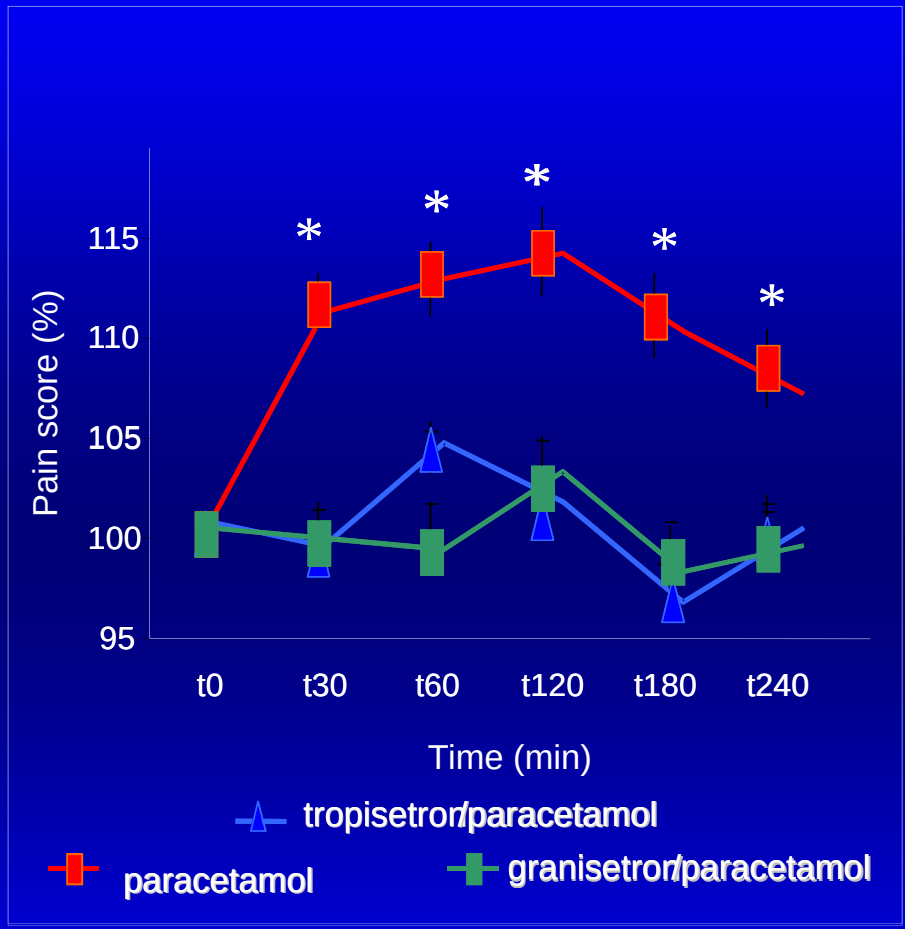


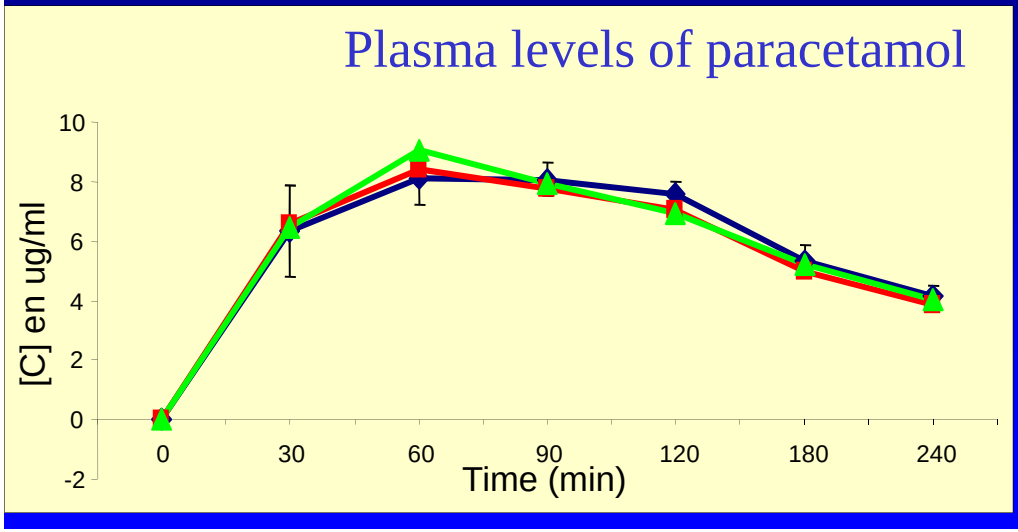
5-HT3



Alloui et al., 2002

MECANISME SEROTONINERGIQUE CENTRAL HOMME



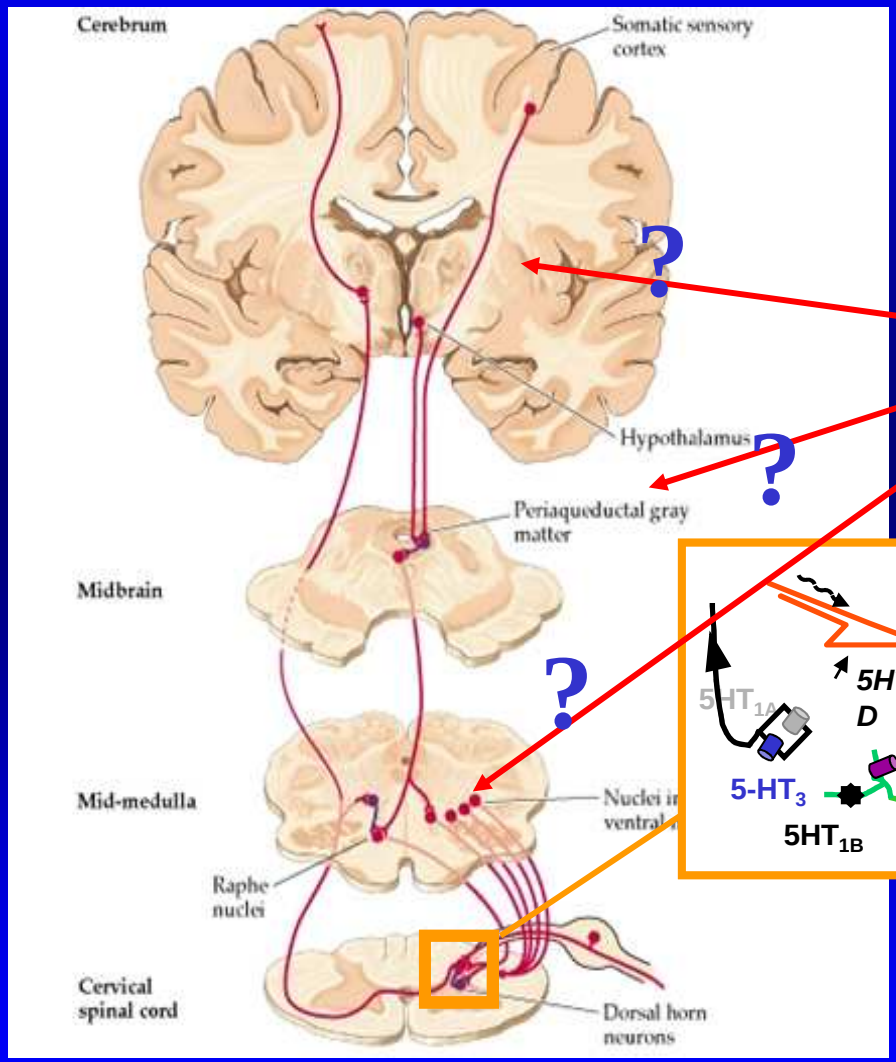


Pickering et al., 2006

Effet du prétraitement par antisens anti-5HT$_3$ sur l'effet antinociceptif du paracétamol

⇒Pas de réduction de l'effet antinociceptif du paracétamol

Mais des interrogations demeurent en amont et en aval de l'activation sérotoninergique



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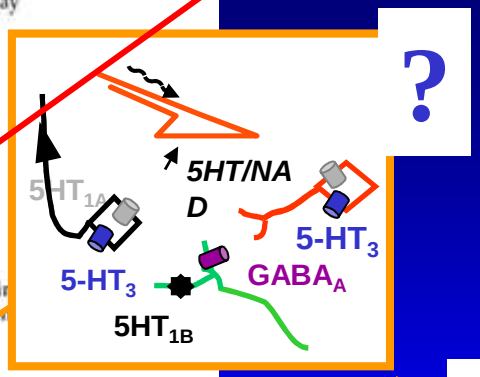
PARACETAMOL ADMINISTRE per os



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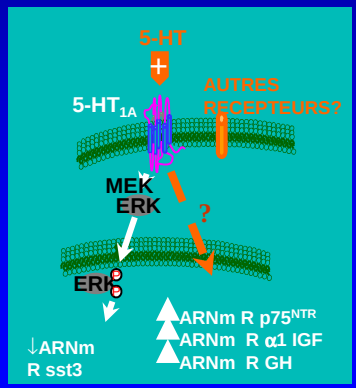


EN AVAL

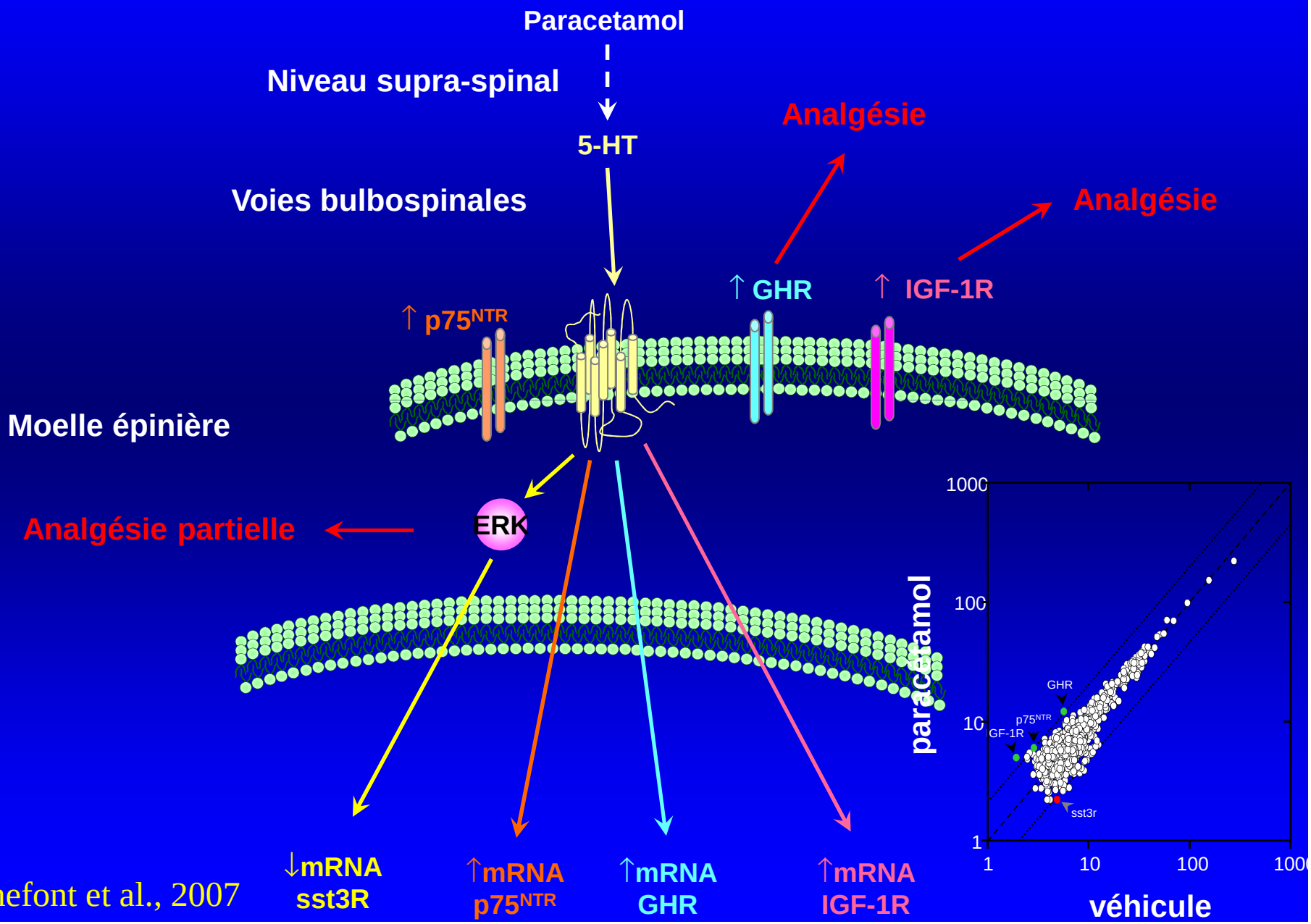
UNE ACTIVATION INDIRECTE DES VOIES SEROTONINERGIQUES

PAS DE LIAISON (Raffa et al.1996; Pélissier et al, 1996)

UNE AUGMENTATION DE LA LIBERATION DE 5-HT CENTRALE

(Pini et al, 1997; Courade et al. 2001)

DES EFFETS INTRA-CELLULAIRES COMPLEXES

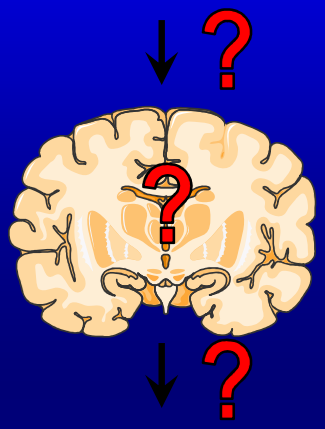


Bonnefont et al., 2007

EN AMONT

Paracétamol per os

Cerveau



Tronc cérébral

Voies sérotoninergiques

Sérotonine

Moelle épinière

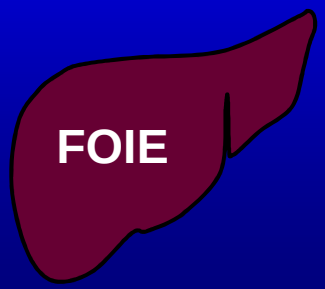
Récepteurs5-HT

- Augmentation de l'activité ERK
- changement de l' expression de gène
- Implication de l'axe GH/IGF-1

Analgésie

LE PARACETAMOL EST METABOLISE

Högestatt et al. 2005



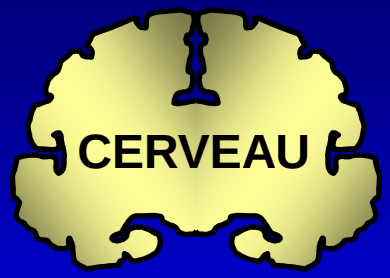
Paracétamol

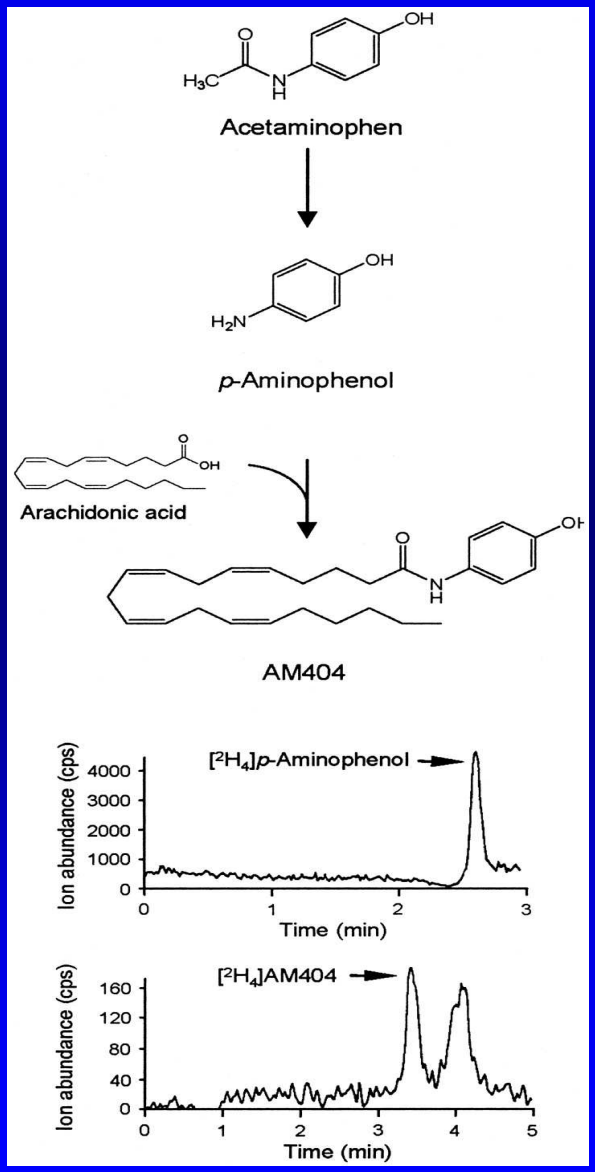
↓ Déacétylases

p-aminophénol

↓ AA FAAH

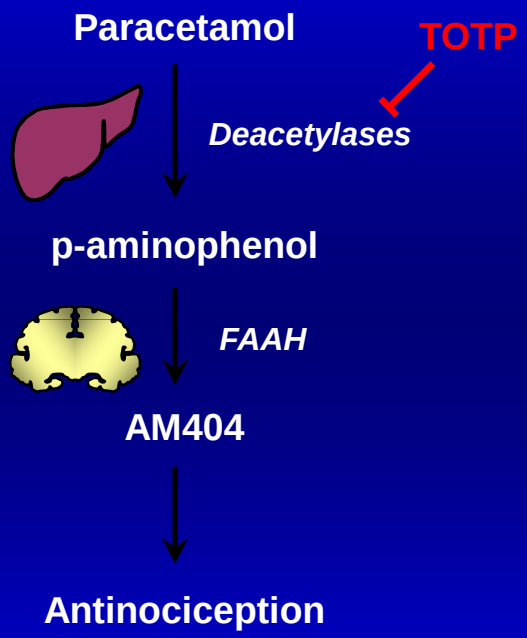
AM404

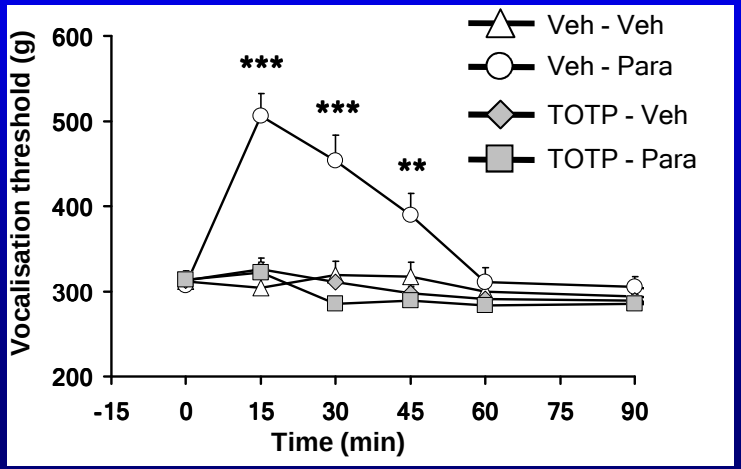


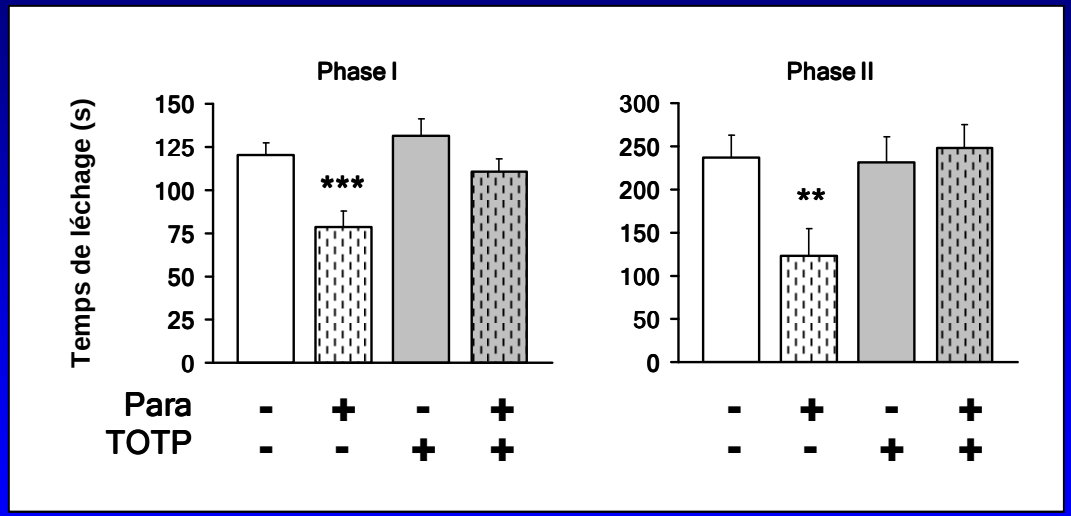


Est-ce que ces voies métaboliques sont impliquées dans l'effet du paracétamol?

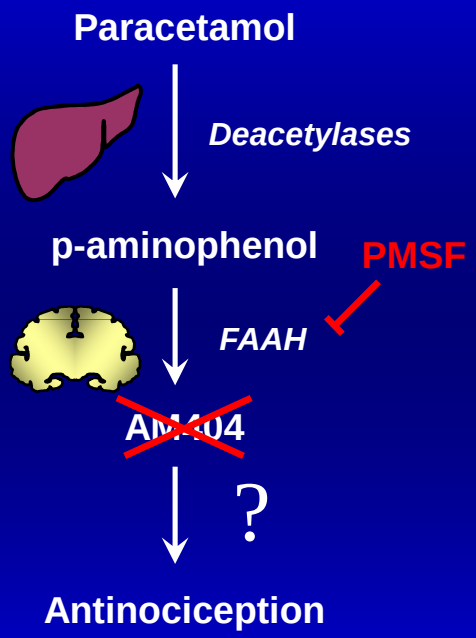
LE PARACETAMOL AGIT *via* LE P-AMINOPHENOL

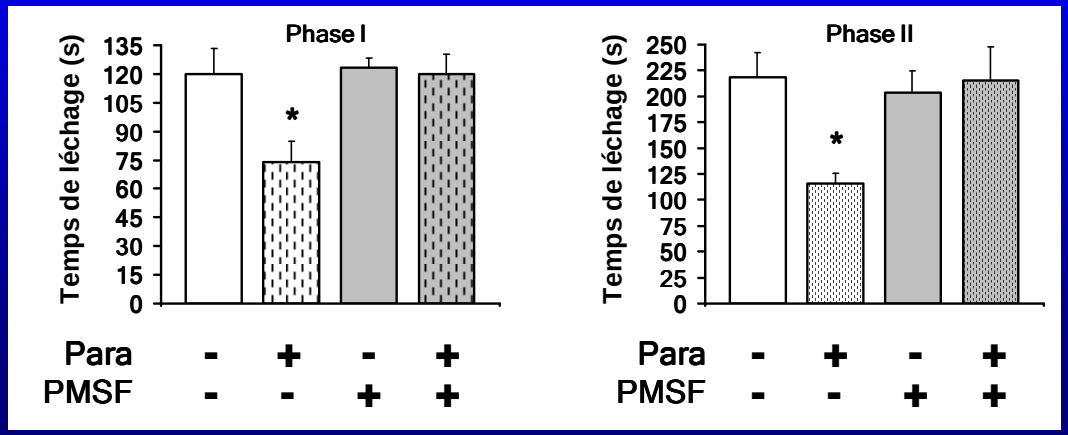


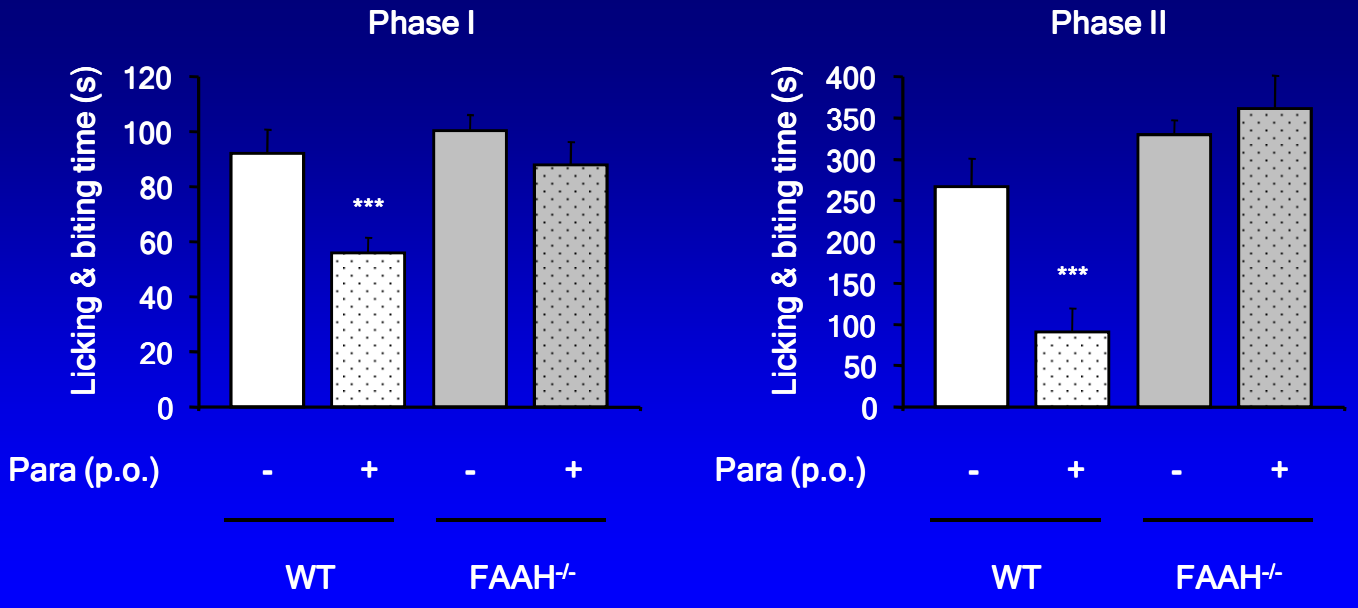




LE PARACETAMOL AGIT *via* L'AM404

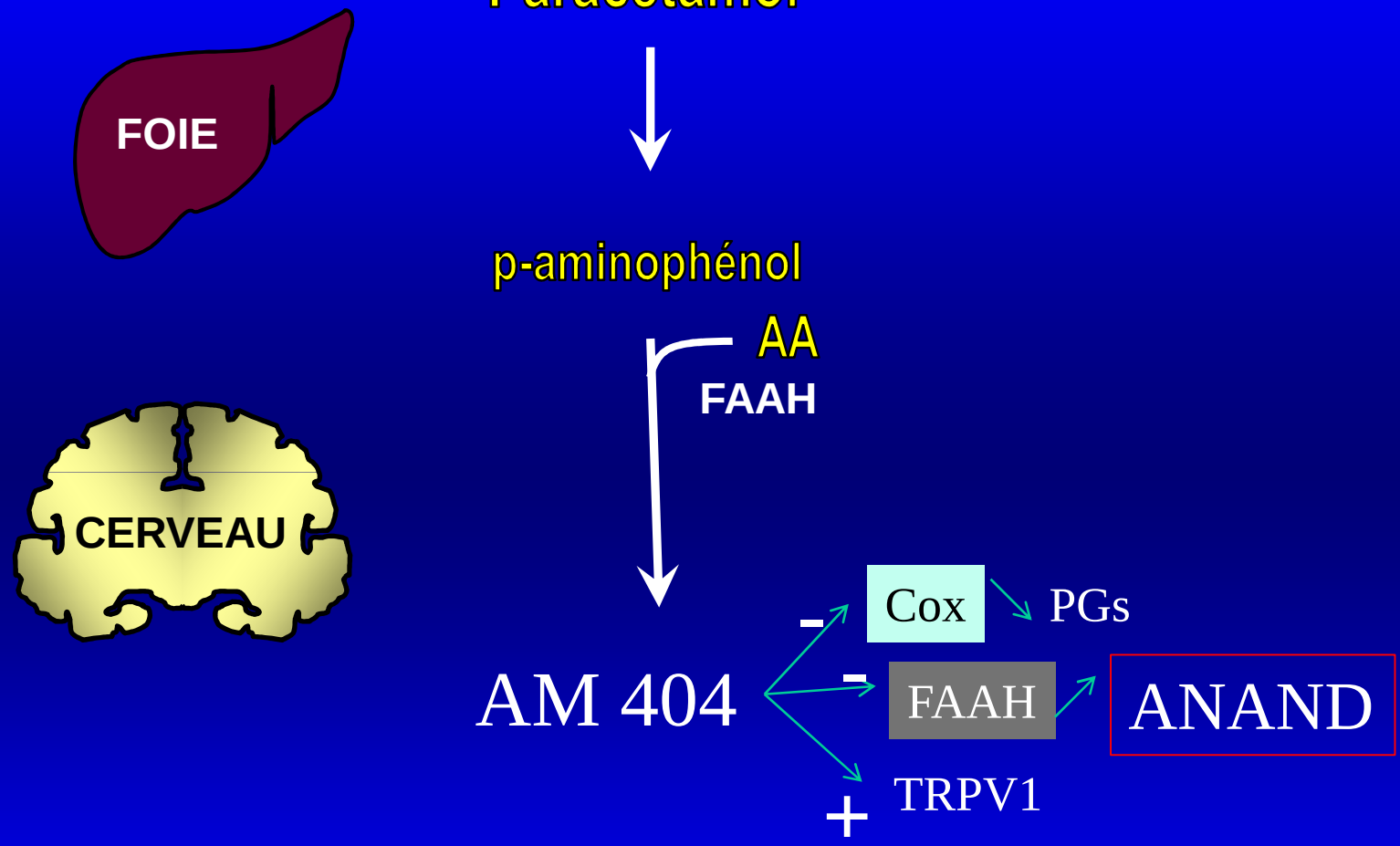






Hogestatt et al., 2005

Di Marzo and Deutsch, 1998



LE PARACETAMOL AGIT *via* LES RECEPTEURS CB1

Paracétamol

Deacetylases

p-aminophénol

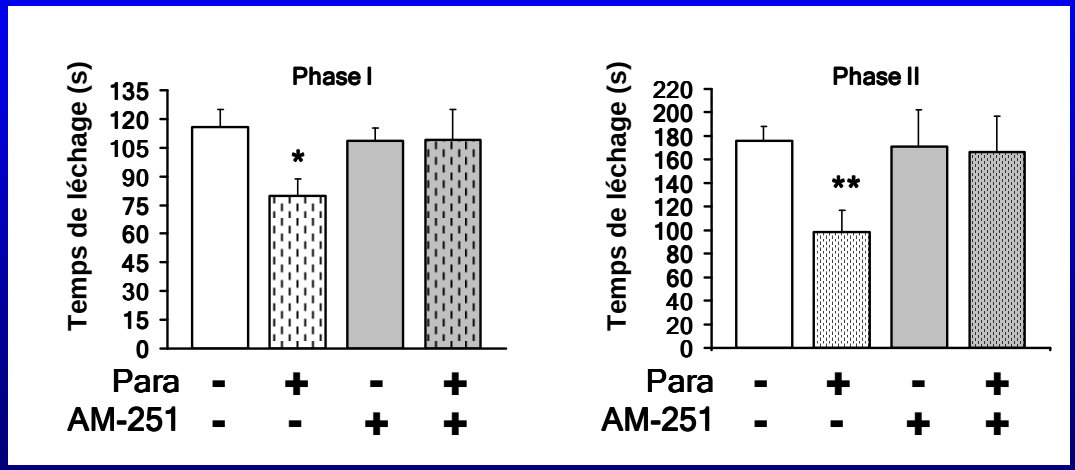
FAAH

AM404

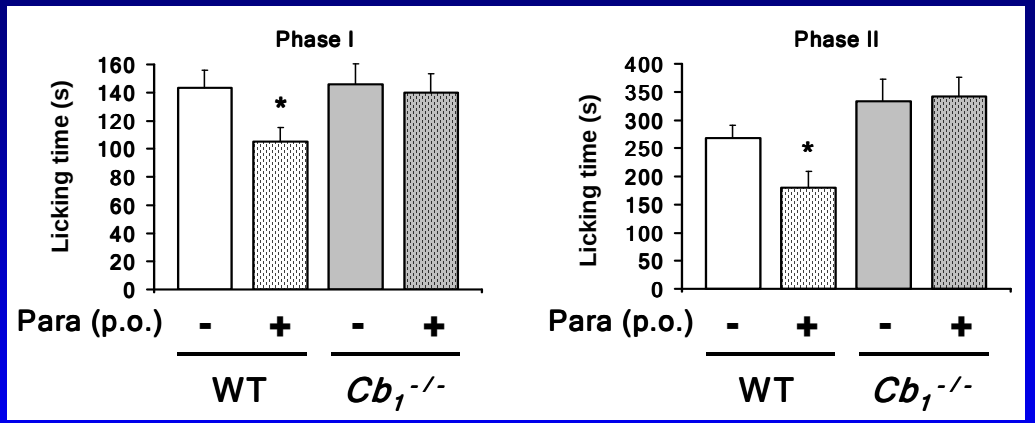
AM-251

Activation du système endocannabinoïde

Antinociception



Formalin test



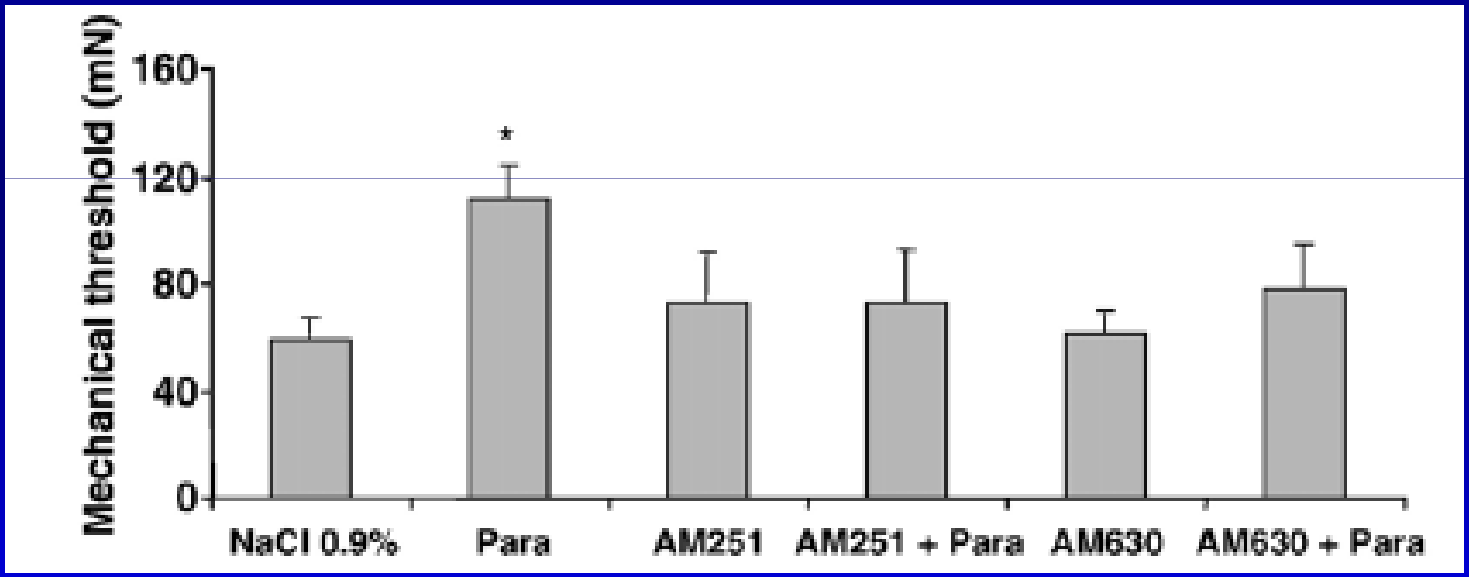
Implication CB1 indirecte

Mallet et al., Pain, 2008

INHIBITION PAR DES ANTAGONISTES CB1

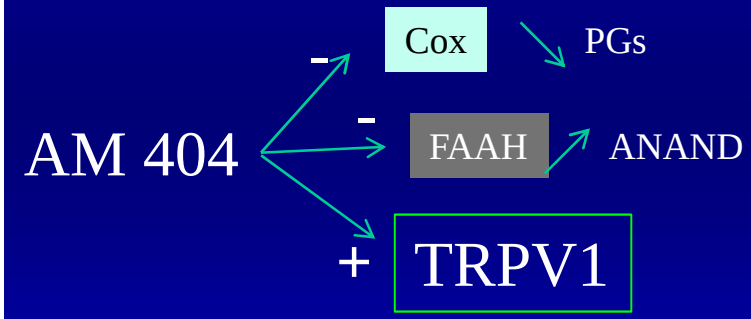
Ottani et al., E. J.P. 2006

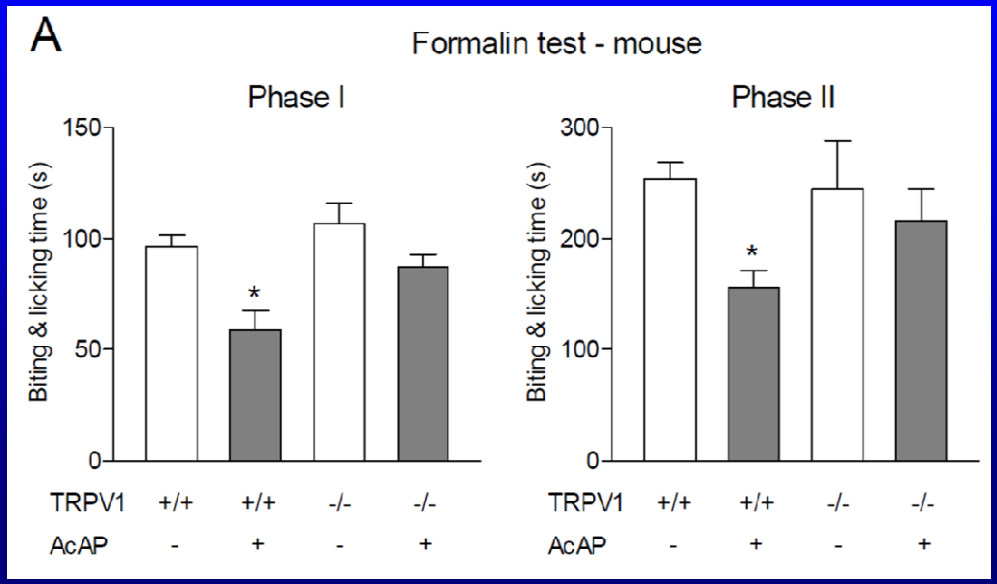
Dani et al., E.J.P. 2007

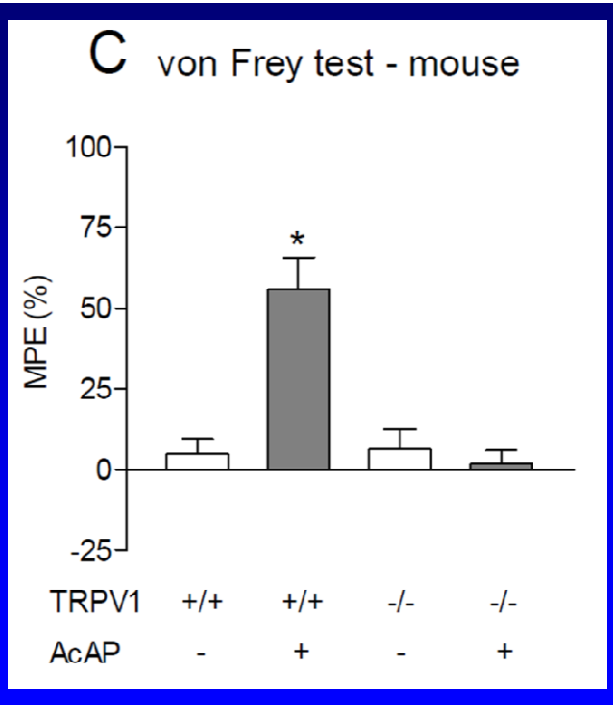


Ligature partielle, von Frey
Effet périphérique du paracétamol

LE PARACETAMOL AGIT *via* CB1 et TRPV1

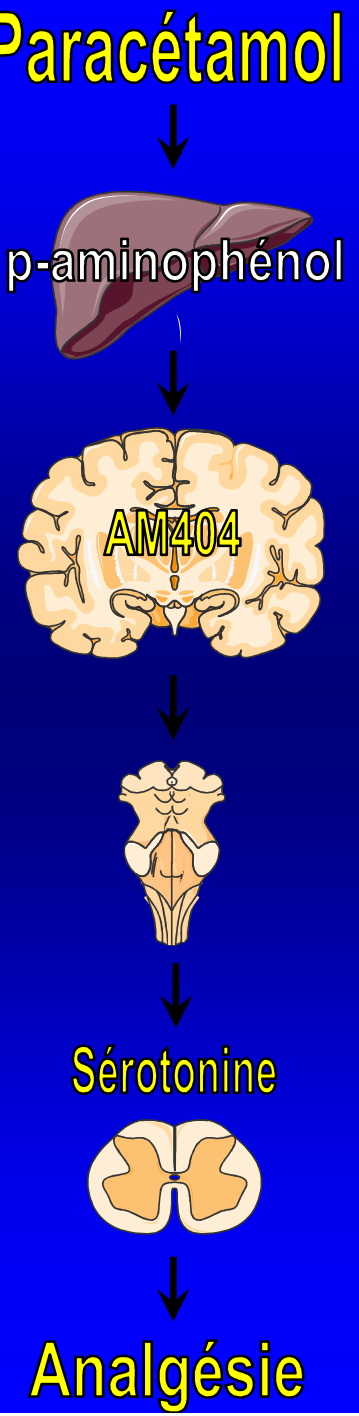






Mallet et al, PLoS ONE, 2010

LIEN ENTRE CB_1 ET SYSTÈME 5-HT ?



Système Cannabinoïde TRPV1

?

Système sérotonergique

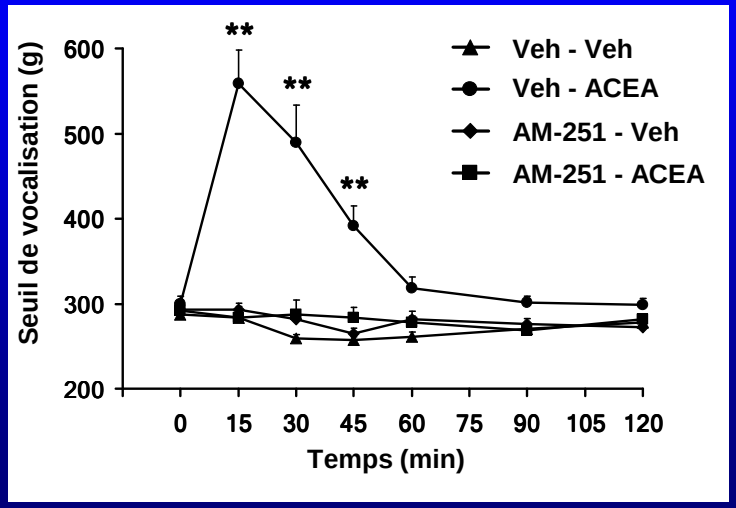
5-HT récepteurs

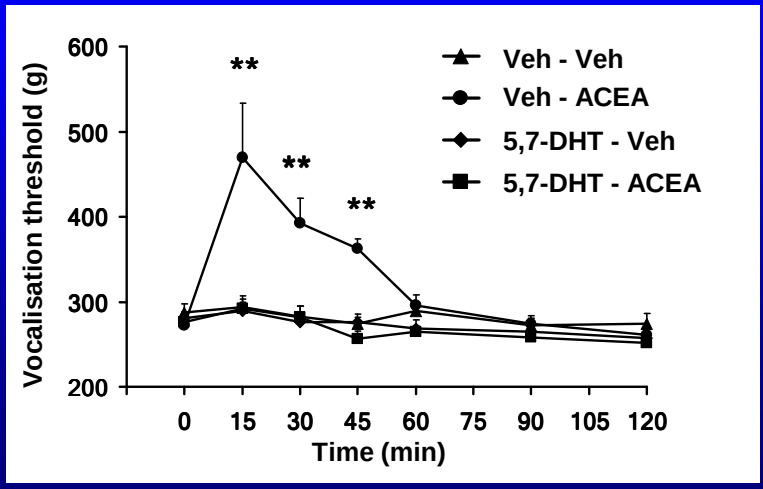
SATIVEX*

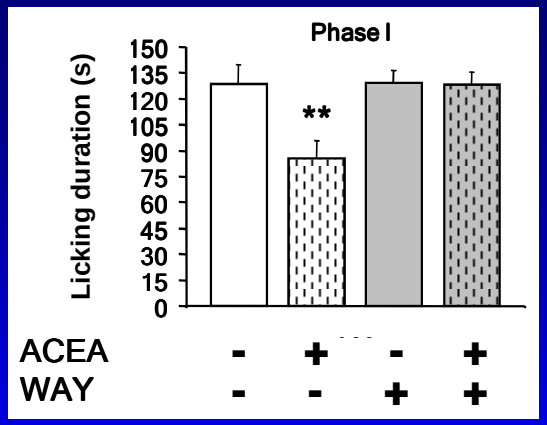
ANTAGONISTES ET AGONISTES TRPV1 en dévt

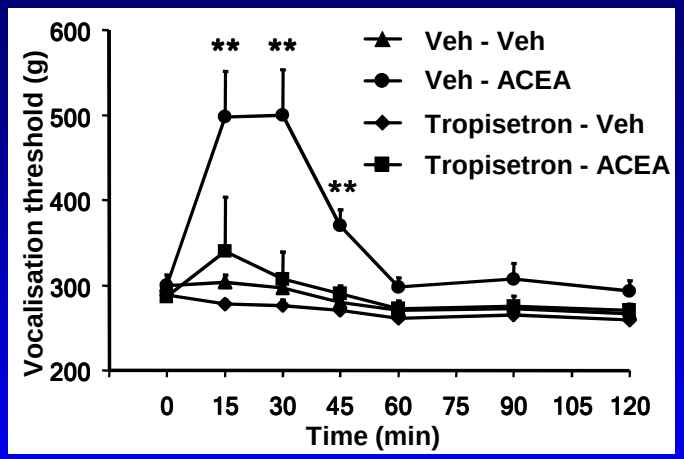
Mallet et al., Pain, 2008

L’agoniste CB1 a le même profil sérotoninergique que le paracétamol

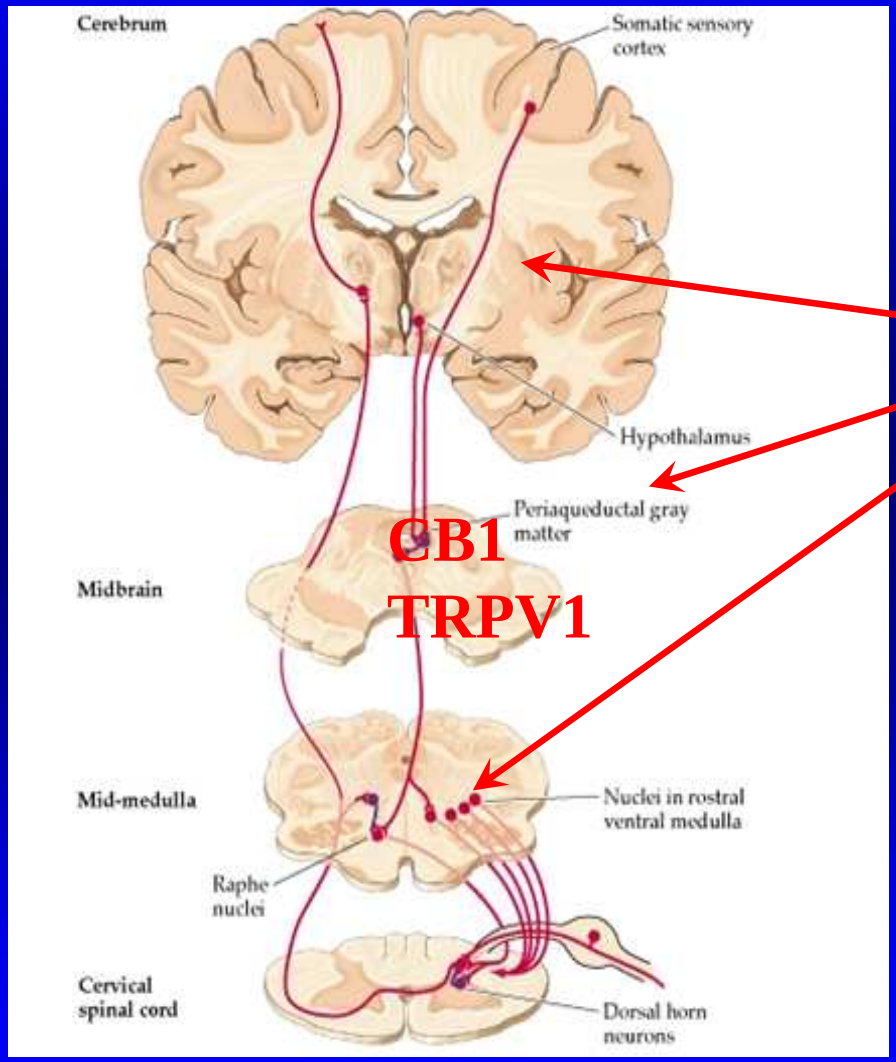




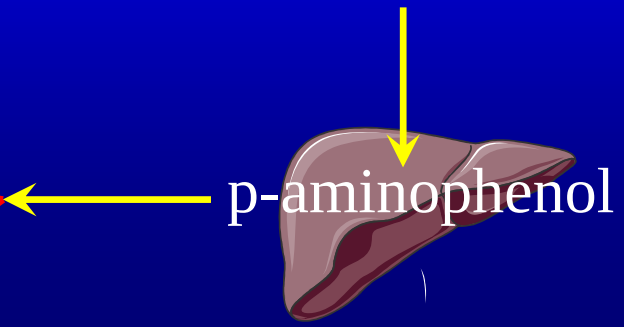




PARACETAMOL: UN PRO-MEDICAMENT?

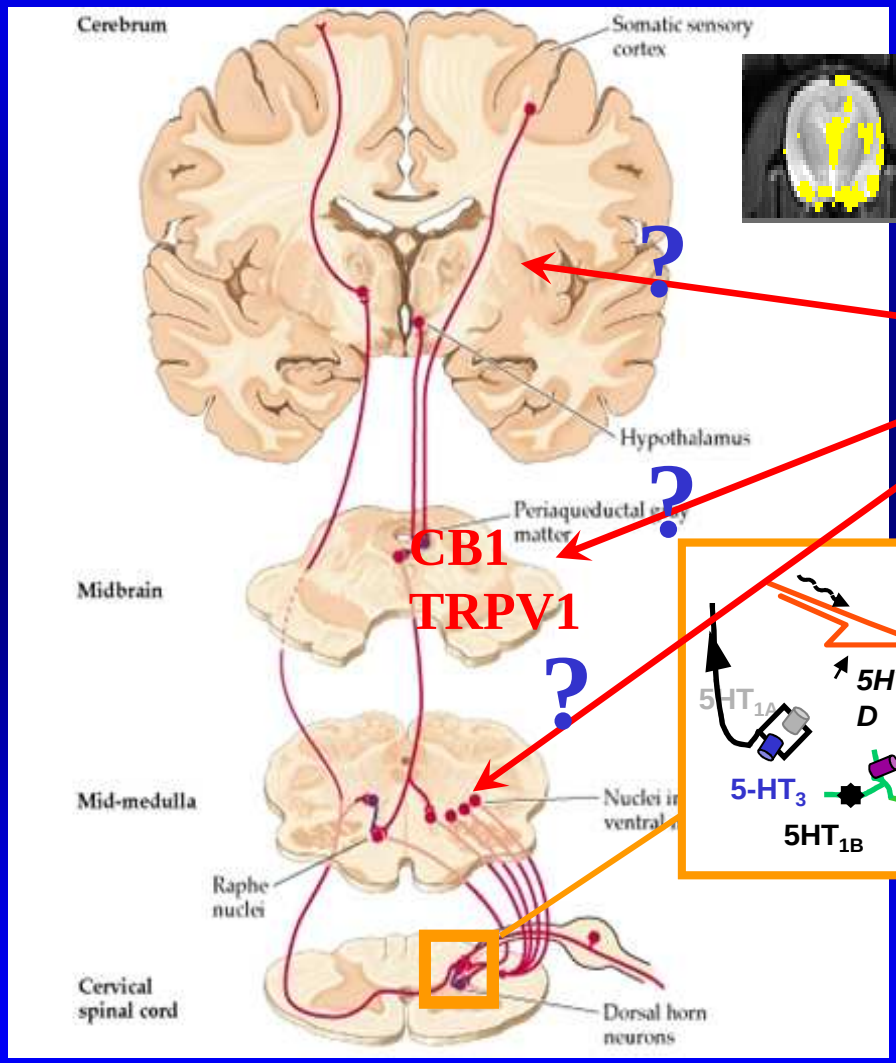


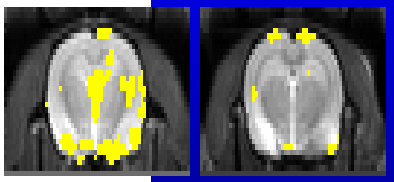
PARACETAMOL *per os*



Efficacité analgésique
Implication des récepteurs CB1
Implication des récepteurs TRPV1
Implication des voies 5-HT
Implication des récepteurs 5-HT

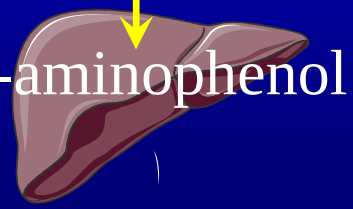
MECANISME D'ACTION DU PARACETAMOL: DES INTERROGATIONS DEMEURENT

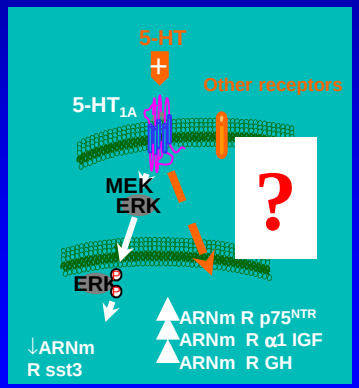




PARACETAMOL *per os*

iv ?

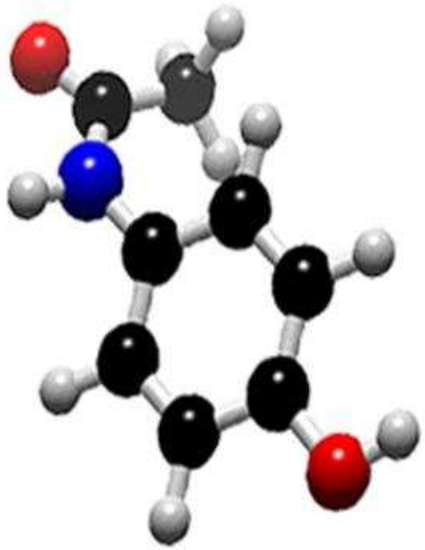




CONCLUSION

P R O - D R U G

CARTE NATIONALE D'IDENTITÉ N° : 070143300203

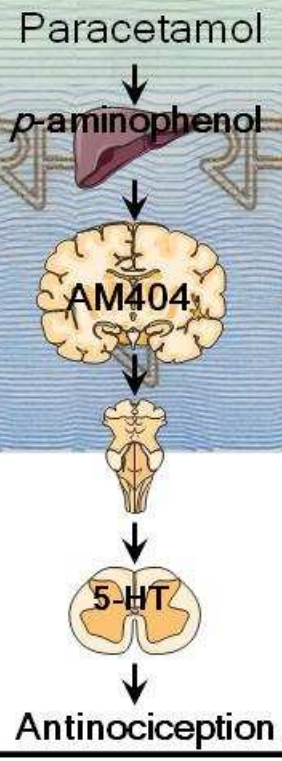


Name : PARACETAMOL / ACETAMINOPHEN

Site of action : Central Nervous System

Mechanism of action :

- ~~COX inhibitor~~
- Endocannabinoid System
- TRPV1
- Serotonergic System



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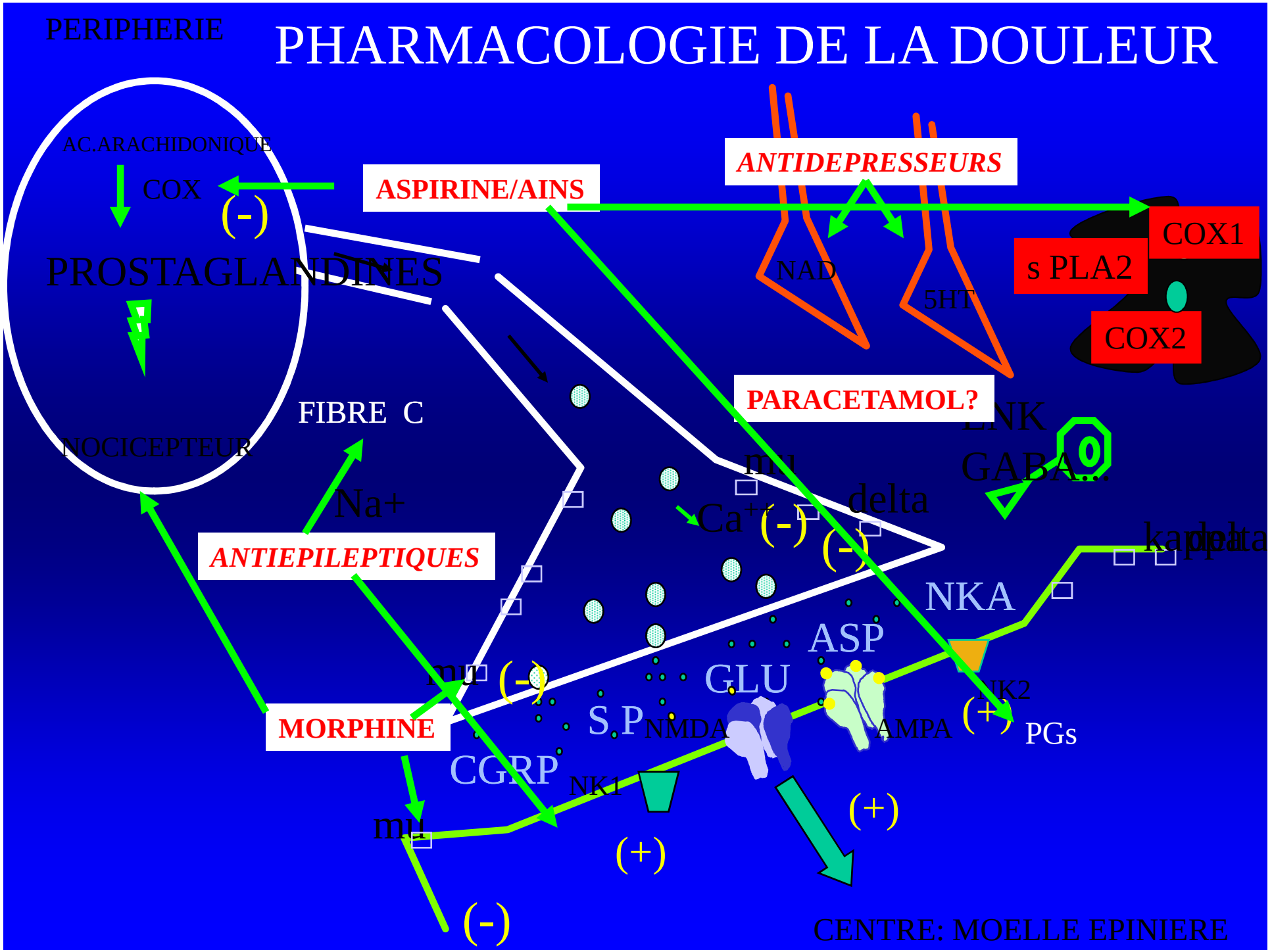
PERIPHERIE
PHARMACOLOGIE DE LA DOULEUR
AC.ARACHIDONIQUE
COX
(-)
PROSTAGLANDINES
NOCICEPTEUR
ASPIRINE/AINS
ANTIDEPRESSEURS
NAD
5HT
COX1
s PLA2
COX2
PARACETAMOL?
FIBRE C
Na+
ANTIEPILEPTIQUES
mu
Ca++
(-)
delta
ENK
GABA...
kappa
NKA
ASP
GLU
S.P
NMDA
AMPA
NK2
(+)
PGs
CGRP
NK1
MORPHINE
mu
(+)
(-)
CENTRE: MOELLE EPINIERE

CONCLUSION

DES ETUDES A POURSUIVRE

MAIS QU'APPREND-T-ON (outre son profil)?:

* effet opposé de l'activation TRPV1 entre périphérie et centres

* plusieurs impacts de l'inhibition de la FAAH

* intérêt des médiateurs lipidiques

* interactions entre récepteurs CB1 et TRPV1

* modulation des voies bulbospianles par différents médicaments

PARACETAMOL

UN PRODUIT D'ACTUALITE:

* Consommation
* Analyse de son hépatoxicité
* Analyse de son mécanisme d'action

UN PRODUIT D'AVENIR:

* Source d'innovation thérapeutique

Collaborations

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Patrick Beaune (Paris)
Marie-Ange Loriot (Paris)
Teresa Pelissier (Santiago)
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