

**ÚJ IRÁNYZAT AZ OPIOID  
FAJDALOMCSILLAPÍTÓK KUTATÁSÁBAN:  
PERIFERIÁS TÁMADÁSPONTÚ  
MOLEKULÁK KÉMIÁJA ÉS  
FARMAKOLÓGIÁJA**

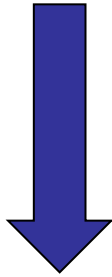
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Semmelweis Egyetem  
Farmakológiai és Farmakoterápiás Intézet  
2015

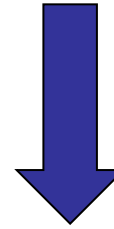
# CLASSIFICATION OF PAIN

many ways to classify pain



## Based on cause

- Acute injury (Nociceptive pain)
- Inflammatory pain
  - Subacute
  - Chronic
  - Tumor?
- Neurogenic pain
  - Neuralgic pain
  - Neuropathic pain
  - Primary headache syndromes  
(migraine, cluster)
  - Tumor?

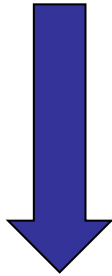


## Based on pain duration

- Acute pain
- Chronic pain

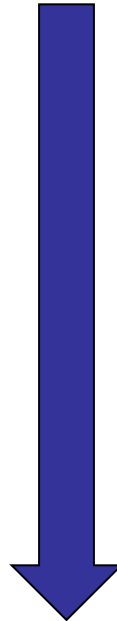
# CLASSIFICATION OF PAIN

many ways to classify pain



## **Nociceptive**

Somatic  
Visceral

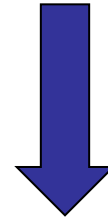


## **Neuropathic**

disease or lesion in the somatosensory n.

- hyperalgesia or allodynia
- paresthesias (tingling)

(spinal cord injury, diabetic neuropathy,  
postherpetic neuralgia, post-stroke pain  
, phantom pain)



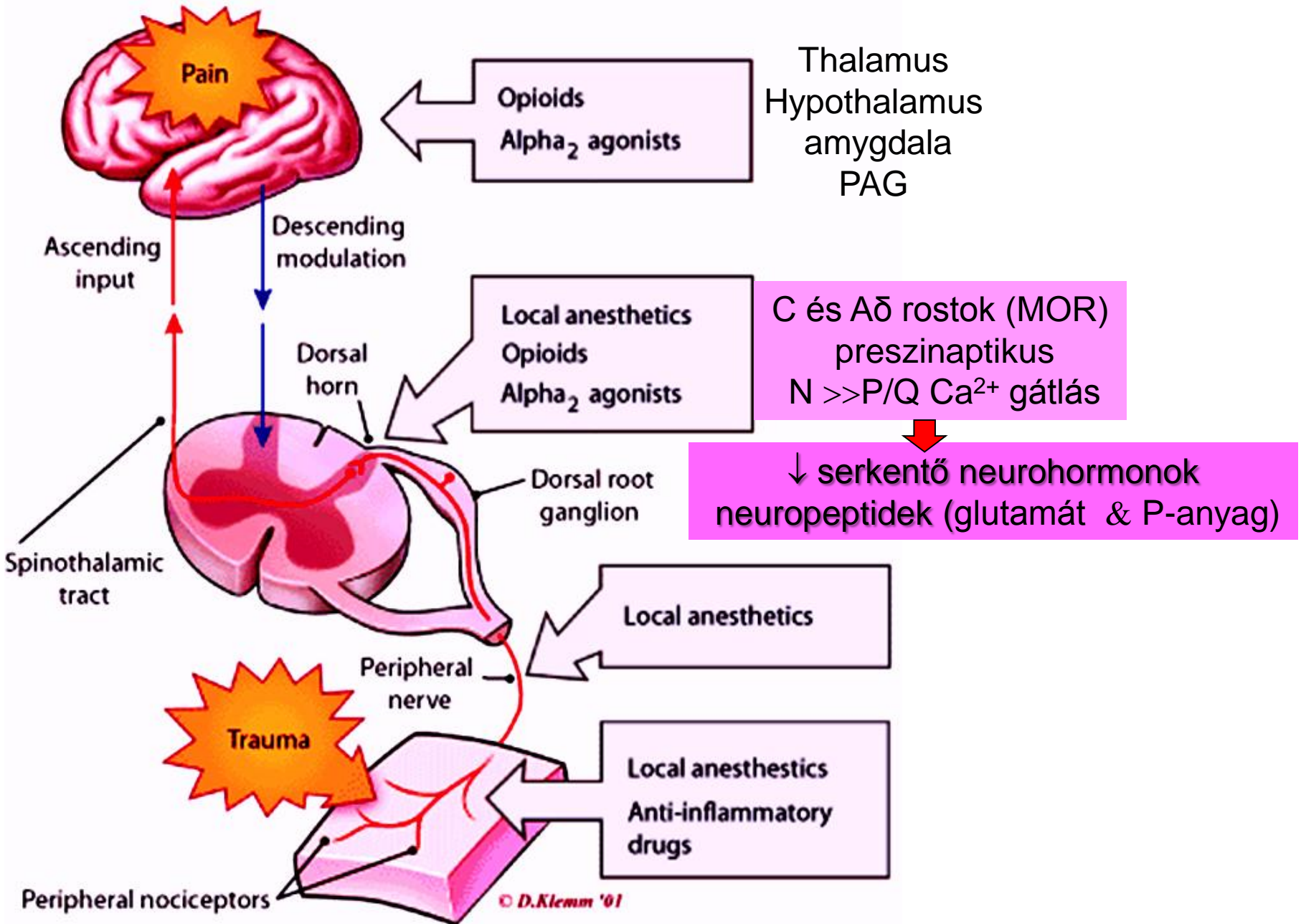
## **Inflammatory**

evoked by proinflammatory m.

Many  
acid

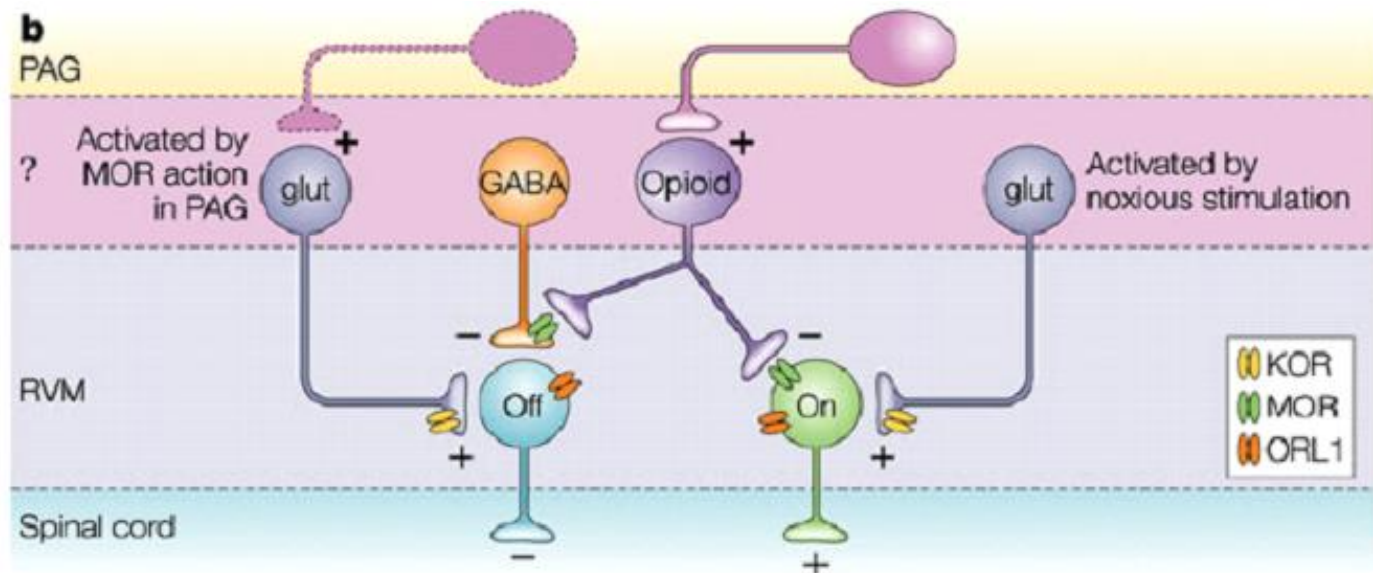
activation & sensitization of  
nociceptive pain pathway

# THE TARGETS OF ANALGESIC AGENTS



# THE TARGETS OF OPIOID ANALGESICS

- ❑ Periphery nerve terminals: low OR reserve, only drugs with high intrinsic efficacy might have analgesic effect than low efficacy opioids.
- ❑ Spinal cord dorsal horn outer laminae (I és II) – primary site for it. administered opioids.
- ❑ Periaqueductal grey matter (PAG) in brain stem



# PAIN TRANSMISSION

- from the periphery by  $A\delta$  and C fibers.

On the peripheral terminals partially identified mechanisms taking up the stimulus

- TRPV1 (capsaicin sense): heat and low pH
- TRPV2: heat
- ASICs channels: low pH
- TRPM8 (menthol): cold
- TRPA: chemical irritants (acids)
- Transient receptor potential ankyrin 1 mustard oil
- ENaC (Epithelial Na channel): mechanical stim.
- Mechanosensitive K channels (KCKN family: TREK and TRAAK channels): mechanical stimulation
- ATP  $P_{2x3}$  receptor: mechanical (cell) injury, Located on  $A\delta$  fibers

# OPIOID RECEPTOROK

G-protein-kapcsolt

$\mu$  (MOR)

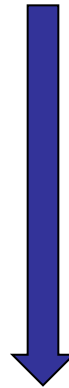


$\mu_1$  (fájdalomérző pálya)

$\mu_2$  (légzőközpont)

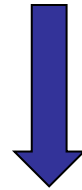
$\mu_3$  (immunsejtek)

$\kappa$  (KOR)



$\kappa_{1a}$ ,  $\kappa_{1b}$ ,  $\kappa_2$ ,  $\kappa_3$

$\delta$  (DOR)



$\delta_1$  és  $\delta_2$

**Aktiváció**

adenilát-cikláz gátlás

↓ cAMP

feszültségfüggő  $Ca^{2+}$  zárás

$K^+$ -csatornák nyitás

preszinaptikus  
idegvégződésekben

posztzinaptikus n.

**TISSUE DAMAGE**



**RELEASE INFLAMMATORY  
MEDIATORS**

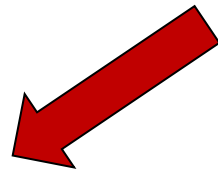
Bradykinin

serotonin

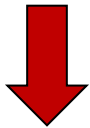
prostaglandins

Cytokines

H<sup>+</sup>



↓ threshold



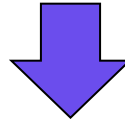
**Less stimuli**

primary sensitisation

nociceptors stimulation

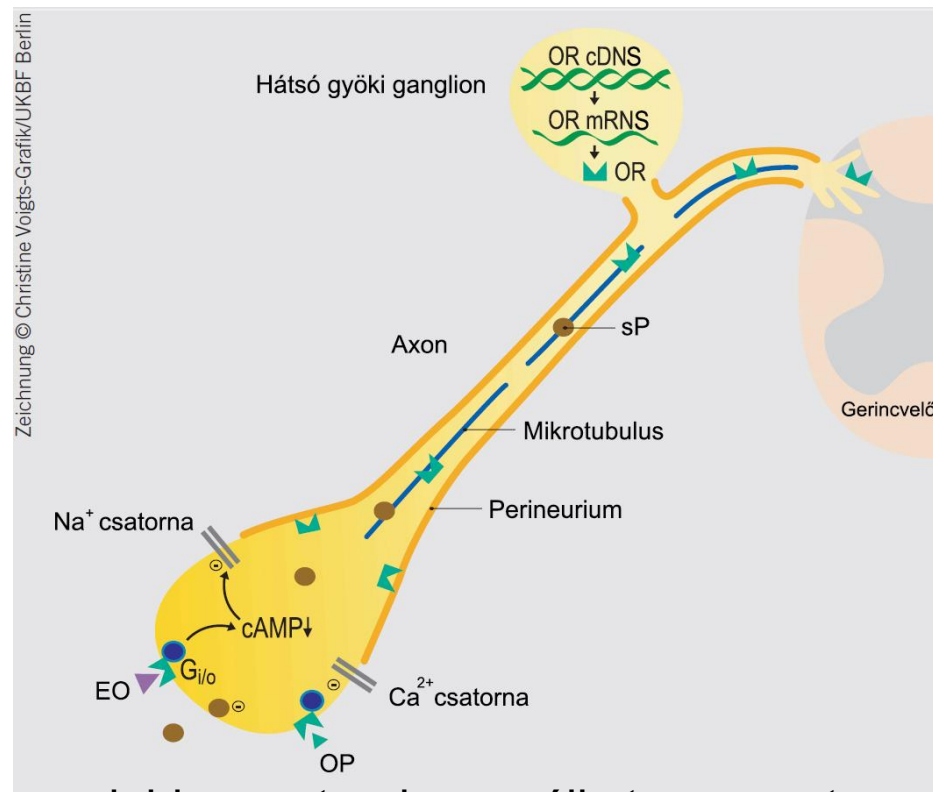


# PERIFÉRIÁS OPIOID RECEPTOROK



Immunsejtek

Centrális & perifériás elsődleges érző n.  
hátsógyöki ganglion



opiooid receptorok axonális transzport

# Local tissue acidosis & painful states

In peripheral tissues, acidic pH can directly excite nociceptive neurons by activating:

- Acid-sensing ion (Na) channels (ASICs), are considered as one of key ion channels to excite nociceptive neurons.

- **Other channels regulated by acidic pH:**

  - voltage-gated Na<sup>+</sup>, K<sup>+</sup> and Ca<sup>2+</sup> channels

  - transient receptor potential vanilloid 1 (TRPV1)

  - (Wemmie et al., 2006 and Holzer, 2009),

- Tetrodotoxin-resistant (TTX-R) Na<sup>+</sup> channels

  - expressed on small- and medium-sized sensory neurons (DRG and trigeminal ganglia)

  - have role in inflammatory, NP and cold pain.

  - (Zimmermann et al., 2007, Eijkelkamp et al., 2012 and Waxman and Zamponi, 2014).

- TTX-R Na<sup>+</sup> inhibited KOR agonists via an opioid receptor-independent mechanism.

# MOLECULAR MECHANISMS

Damage of peripheral sensory fibers results in:

↑ expression of the following:

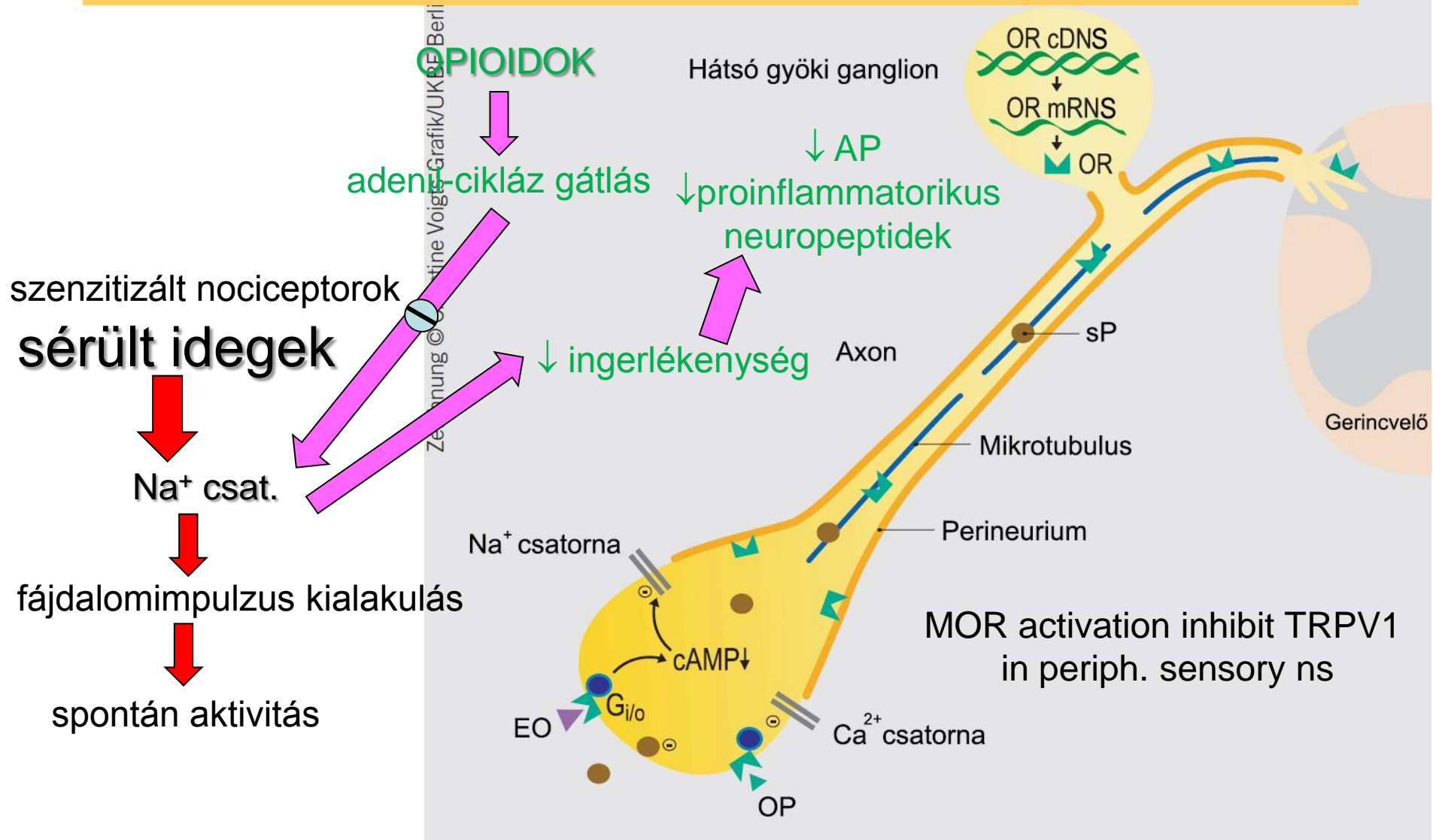
(in myelinated neurons contribute to hyperalgesia)

- $\text{Ca}_v\alpha 2\delta\text{-1}$  channel subunit
- $\text{Na}_v 1.3$  sodium channel (1nM TTX)
- Bradykinin (BK) B1 and capsaicin TRPV1 receptors

Down regulation of the following:

- $\text{Na}_v 1.8$  Na channel (100 $\mu\text{M}$  TTX)
- B2 receptor, substance P (SP), MORs in unmyelinated ns.

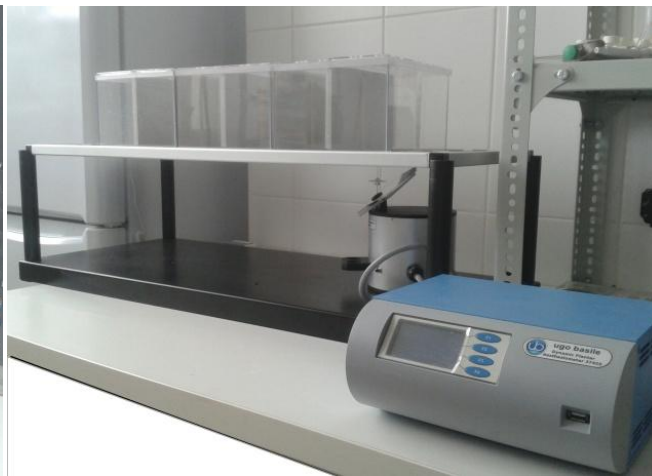
# PERIFÉRIÁS OPIOID RECEPTOROK



OR: capsaicin receptorral rendelkező viscerális rostokon  
P-anyagot, CGRP-et és izolektin B4-et szintetizáló n. (Borgland 2001).

# ANIMAL PAIN MODELS

- Acute pain: Heat, chemicals -induced pain.
- Chronic pain: CFA, Streptozocin and nerve injury induced pain.



# Acute nociceptive tests

## Thermal pain tests

- **Radiant heat Tail Flick test** (strong beam to the tail): spinal reflex.

- is not useful for measuring hyperalgesia

- is used for testing opioids

- **Tail Immersion test**

- Dipping the tail into warm water

- **Classic hot plate test**

- The animal is put on a 55 °C warm plate

- It is a more complicated reflex

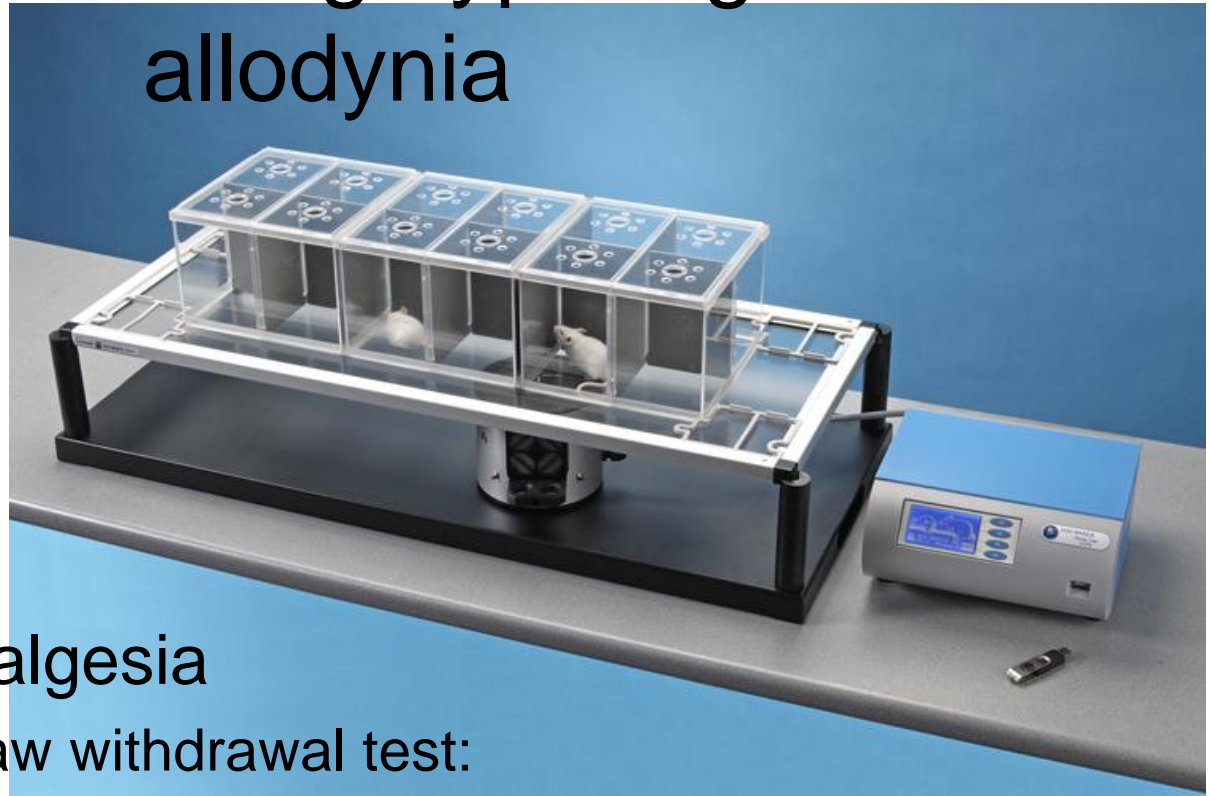
Tail flick and hot plate tests were the only tests used for screening analgesic agents in the preclinical study until the late 1970.



# Acute nociceptive tests

- Cold induced pain
  - Rarely used for acute pain: the paw or tail of the animal is put in cold solution or put on cold surface
- Mechanic induced induced pain
  - Tail pinch test: the tail is put between a plate and a cogwheel like structure and it sets increasing force on it – used sgt. For testing  $\kappa$  opioids
- Electronic impulse induced pain
  - Short electronic impulse on the tail or dental pulp. Sometimes on the surface of the cage. The starting of vocalization is measured.

# Tests for measuring hyperalgesia and allodynia



- Test methods
- Thermal hyperalgesia
  - Haargraves paw withdrawal test:
    - The plantar surface of the hind paw is beamed by IR laser. It measures the removing of the paw
    - It can be used for testing NSAIDs and minor analgesics
    - Contralateral paw can used as control



# Test methods for hyperalgesia and allodynia

- Incremental hot plate test:
  - Temperature of the plate is starting from room temperature and increases
  - Latency and threshold temperature is also measurable
  - No contralateral control
  - It can be used also as cold plate for cold allodynia
- Incremental water bath
  - The fast increase of the bath is difficult to perform
  - The paw sensitivity is tested and contralateral can used as control
- Cold allodynia test:
  - The paw is dipped into ice water and withdrawal latency is measured



# TESTS FOR MEASURING HYPERALGESIA AND ALLODYNIA

## **Mechanical hyperalgesia**

- Randall-Selitto (paw-pressure) test
  - Well trained investigator is important
  - Contralateral paw can used as control



# TESTS FOR MEASURING HYPERALGESIA AND ALLODYNIA

Von Frey test – touch sensitivity test

For both hyperalgesia and allodynia

The paw of the free moving rat/mice is stimulated by a filament.

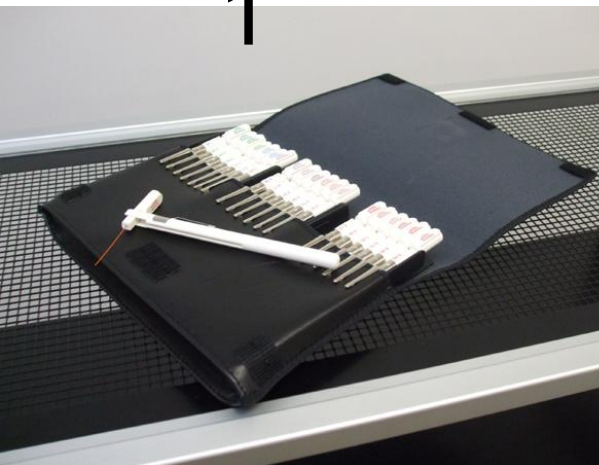
1- Classic

2- Electronic

3- Automatic: Dynamic Plantar Aesthesiometer (DPA)

– Sham or contralateral paws are used as control

1



2



3



# INFLAMMATORY PAIN MODELS

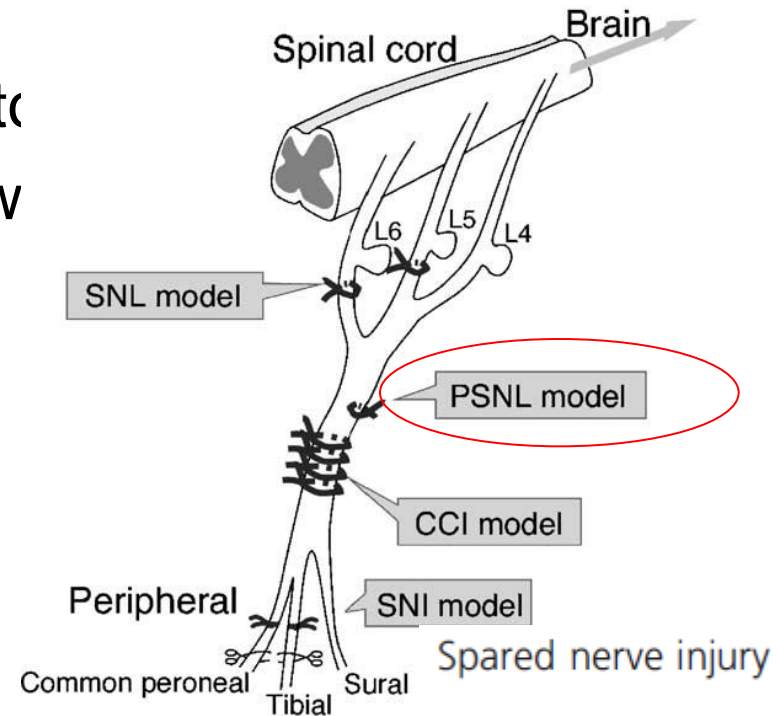
- Carrageenan induced hyperalgesia
  - Subacute inflammation (mechanical hyperalgesia, 3 h), (thermal <3h)
  - For hyperalgesia.
- Capsaicin induced hyperalgesia
  - Capsaicin activates directly TRPV1 receptors on sensory neurons
  - In high dose it can cause desensitization
- Formalin test
  - Intraplantar formalin causes reaction in two phase
    - Phase I. (after ca. 3 min): acute chemical pain
    - Phase II. (after ca. 15 min) : real acute inflammatory reaction
  - It cause spontaneous pain reaction: vocalization and paw licking
  - NSAIDs are active only in phase II.

# INFLAMMATORY PAIN MODELS

- Complete Freund Adjuvant (CFA)
  - M. tuberculosis extract in lipid-water emulsion
  - Evokes arthritis like hyperalgesia (in 3- 14 days)
  - After long period (ca. 3 weeks) in some animals it causes polyarthritis ( is model for RA)
- Acetic-acid writhing test
  - Intraperitoneal injected 0,6% acetic-acid causes spontaneous pain reaction (writhing).
  - Model for visceral inflammatory pain

# Animal models of neuropathic pain

- Peripheral nerve injury models
  - Sciatic nerve injury models
  - **Diabetic neuropathic model**
    - Diabetes is induced by streptozotocin
      - High dose: direct cell toxic, low dose induce immunoreactions
    - Neuropathic symptoms appear in 3 weeks
  - Drug induced neuropathy
    - Pl. Cisplatin, Taxanok

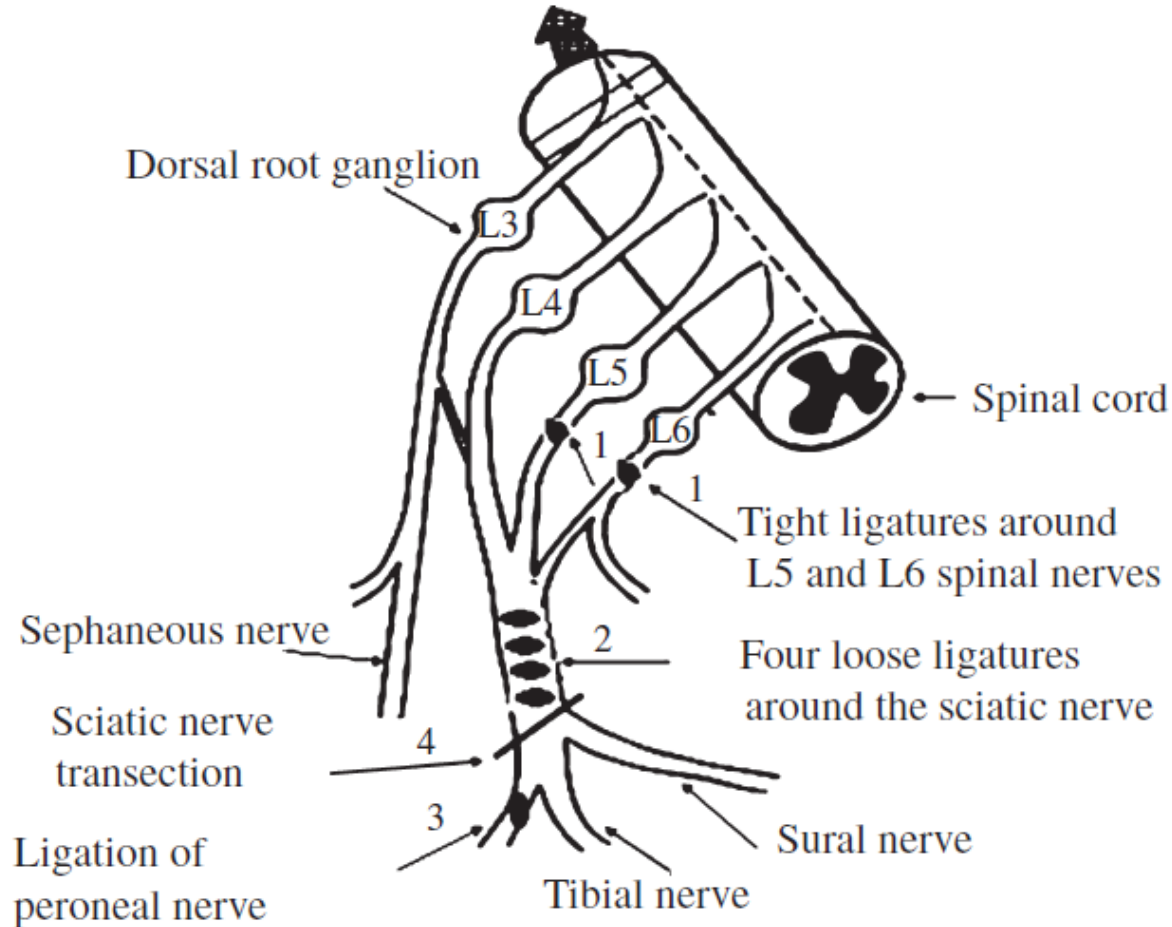


Partial sciatic nerve ligation (PSL/Seltzer model), Pain (1990) 43 205–218.

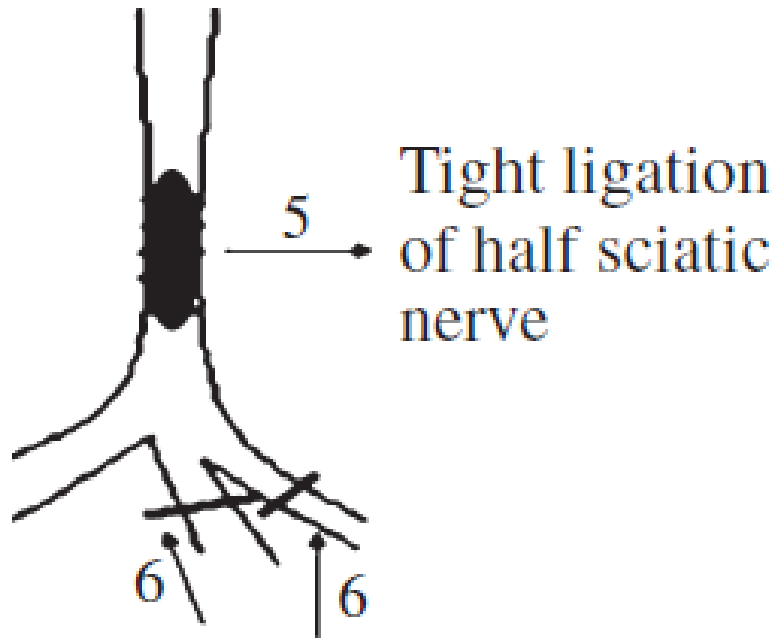
Chronic constriction injury (CCI), Bennett and Xie Pain (1988) 33 87–107.

Spinal nerve ligation (SNL), Kim and Chung, Pain (1992) 50 355–363.

# Animal models of neuropathic pain



# Animal models of neuropathic pain



Transection of tibial and sural nerve



**Table I** List of different animal models of neuropathic pain.

S. no.	Name of model	Principle of injury	Species
1	Axotomy (complete sciatic nerve transection)	Complete transection of sciatic nerve	Rats
2	Chronic constriction injury	Four loose ligatures around sciatic nerve	Rats, mice
3	Partial sciatic nerve ligation (Seltzer Model)	Tight ligation of one-third to half of sciatic nerve	Rats, mice
4	Spinal nerve ligation	(i) Tight ligation of L5, L6 spinal nerves (ii) tight ligation of L7 spinal nerve	Rats, <i>Macaca fascicularis</i>
5	Spared nerve injury	Axotomy of tibial and common peroneal nerves	Rats, mice
6	Tibial and sural nerve transection	Axotomy of tibial and sural nerves	Rats
7	Ligation of common peroneal nerve	Ligation of common peroneal nerve	Mice
8	Sciatic cryoneurolysis	Freezing of the sciatic nerve	Rats
9	Caudal trunk resection	Resection of caudal trunk	Rats, mice
10	Sciatic inflammatory neuritis	Injection of zymosan, HMG, TNF-alpha around sciatic nerve	Rats, mice

11	Cuffing-induced sciatic nerve injury	Implantation of polyethylene cuff around sciatic nerve	Rats, mice
12	Photochemical-induced sciatic nerve injury	Thrombosis in small vessels supplying sciatic nerve by photosensitizing dye and laser	Rats, mice
13	Laser-induced sciatic nerve injury	Radiation mediated reduction in blood supply to sciatic nerve	Rats
14	Weight drop or contusive spinal cord injury	Dropping a weight over the exposed spinal cord	Rats, mice
15	Excitotoxic spinal cord injury	Intraspinal injections of excitatory amino acids	Rats, mice
16	Photochemical spinal cord injury	Thrombosis in blood vessels supplying the spinal cord by photosensitizing dye and laser	Rats
17	Spinal hemisection	Laminectomy of T11–T12 segments.	Rats
18	Drugs-induced		
(a)	Anti-cancer agents (vincristine, cisplatin, oxaliplatin, paclitaxel)	Direct injury of drugs to the nerves of peripheral nervous system	Rats, mice, guinea pigs
(b)	Anti-HIV agents (2,3-dideoxycytidine, didanosine)		Rabbits, rats
19	Diabetes-induced neuropathy	Persistent hyperglycemia-induced changes in the nerves	Rats, mice
(a)	Streptozotocin-induced		
(b)	Genetic models		

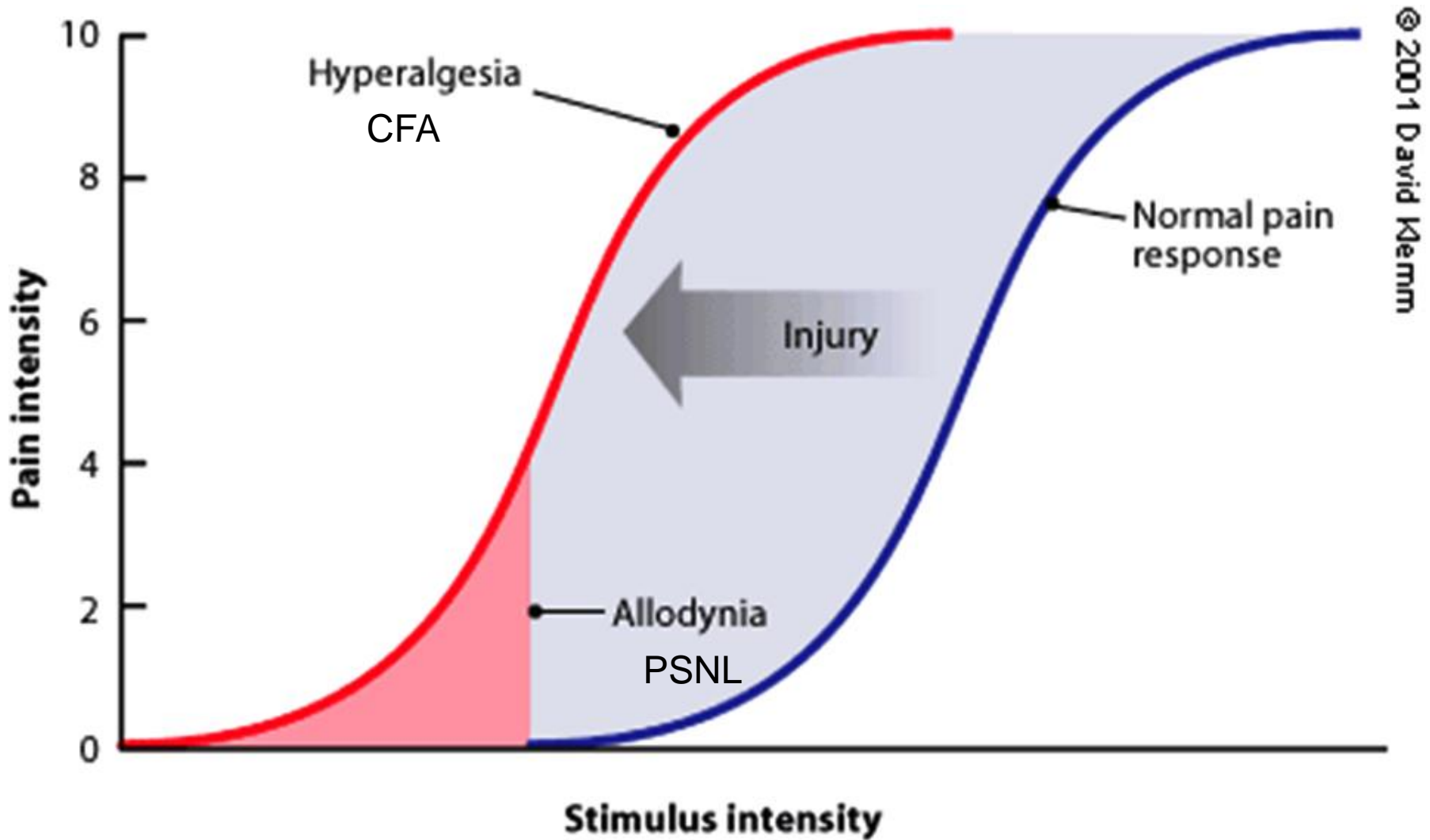
20	Bone cancer pain models		
(a)	Femur, calcaneus,tibial, humerus bone cancer pain	Inoculation of cancerous cells into respective bones	Rats, mice
(b)	Neuropathic cancer pain	Growing a tumor in vicinity of sciatic nerve	Mice
(c)	Skin cancer pain	Injection of melanoma cells in plantar region of hind paw	Mice
21	HIV-induced neuropathy	Delivery of HIV-1 protein gp120 to sciatic nerve	Rats
22	Post-herpetic neuralgia		
(a)	Varicella Zoster virus	Injection of viral infected cells in the footpad	Rats, mice
(b)	Herpes simplex virus	Depletion of capsaicin-sensitive	
(c)	Non-viral model	Afferents with resiniferotoxin	Rats
23	Chronic ethanol consumption/withdrawal	Administration of ethanol over extended period (around 70 days)	Rats
24	Pyridoxine-induced	Administration of high dose pyridoxine for long period	Dogs, rats
25	Trigeminal Neuralgia	Compression of trigeminal ganglion	Rats
		chronic constriction injury to infra-orbital nerve	Rats
26	Orofacial pain	Injection of formalin, carragenan into temporomandibular joints and maxilla	Rats, mice
27	Acrylamide-induced	Administration of acrylamide for prolonged period	Rats

# PAIN TYPES

Types	Source	Innervation	Character.
<b>Visceral</b>	internal organs	C fibres	diffuse and poorly localised, (deep, dull or dragging)
<b>Neuropathic</b>	damaged nerves (in central or peripheral NS). Cause: diabetes mellitus trauma or surgery chemotherapy radiotherapy ischaemia, infection malignancy.		burning or 'like an electric shock

**Allodynia:** Pain may be experienced in response to a stimulus that does not usually cause pain.

**Hyperalgesia:** pain may be a heightened response to a stimulus that is usually painful.



**Allodynia:** Pain may be experienced in response to a stimulus that does not usually cause pain.

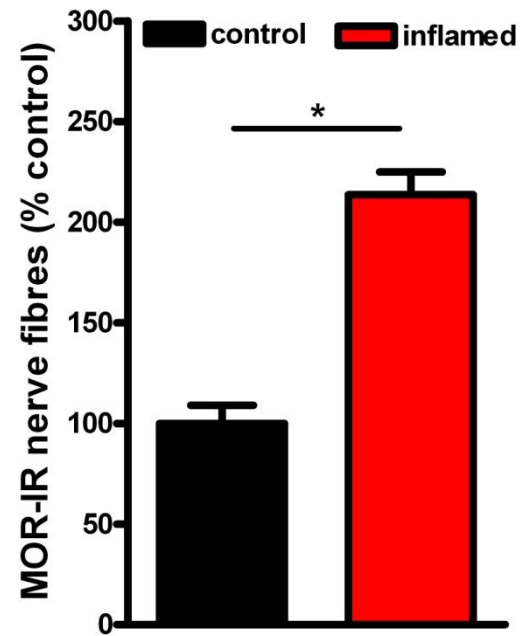
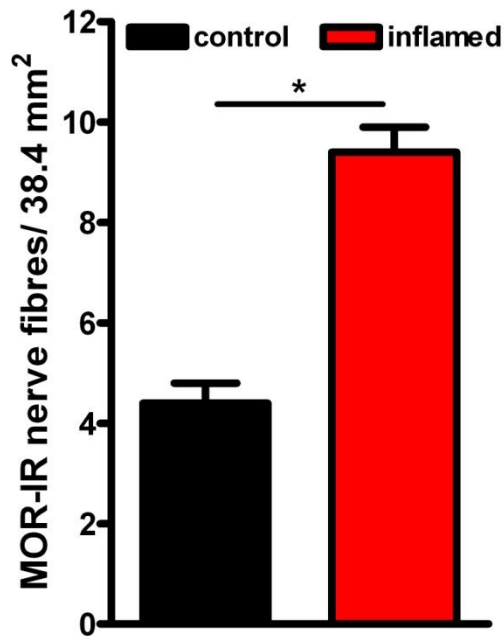
**Hyperalgesia:** pain may be a heightened response to a stimulus that is usually painful.

# PERIFÉRIÁS OPIOID ANALGÉZIA

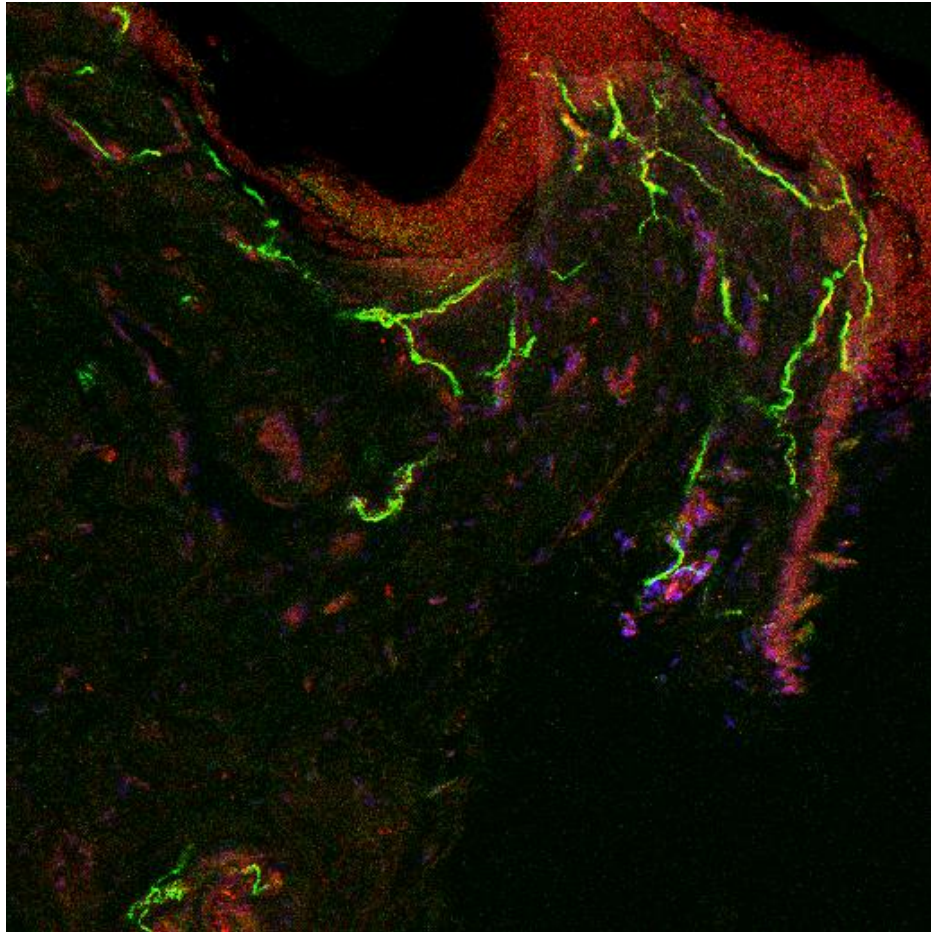
- ❑ The pain relief by perineural morphine injected close to the site of pain generation have been reported by Wood in 1850.
- ❑ Opioid receptors have been reported to be present in the periphery where they might mediate the analgesic action of opioids (*Stein et al., 1995*).

# Inflammation & peripheral opioid receptors

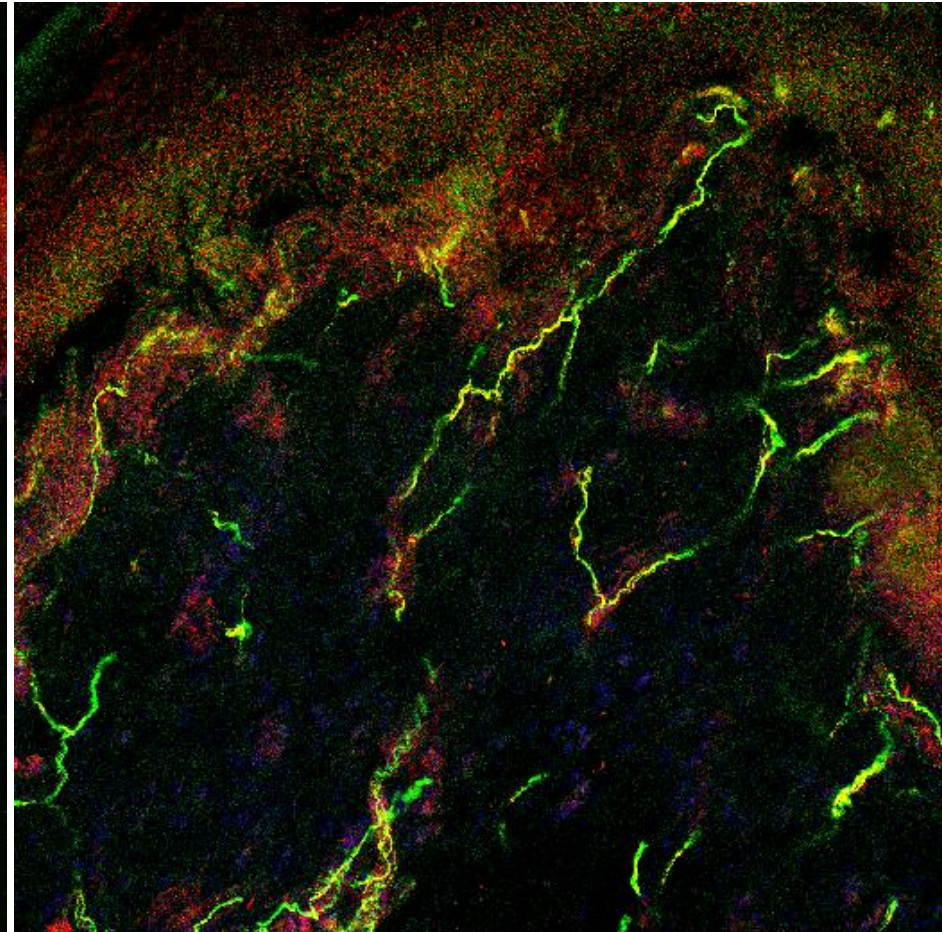
Confocal microscopy shows that MOR-ir is contained in control and inflamed rat paw nerve fibers.



**Control**

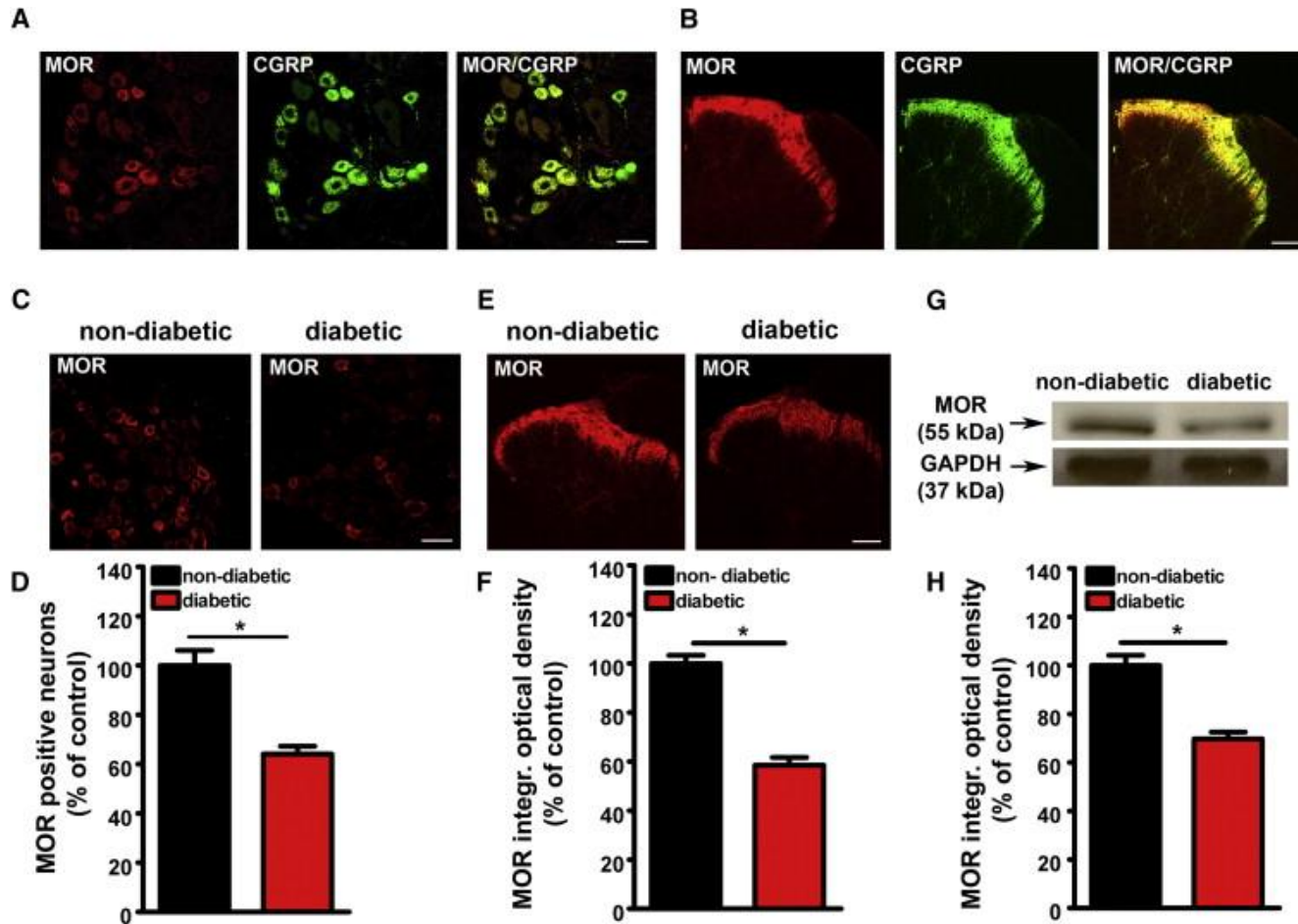


**Inflamed**

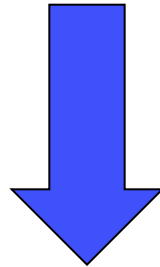




# Diabetes & opioid receptors



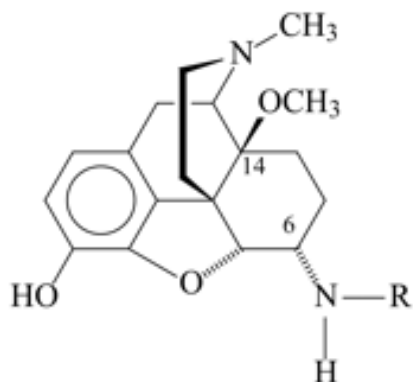
**LOOKING FOR NEW OPIOID ANALGESIC  
AGENTS WITH LIMITED ACCESS TO CNS**



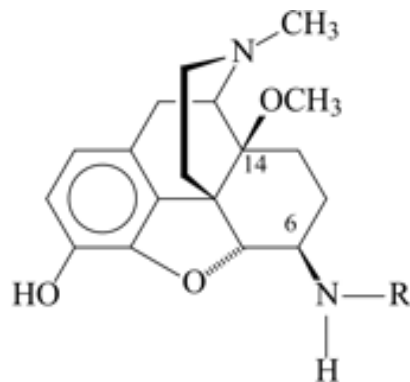
**DECREASES IN THE CNS SIDE EFFECTS OF OPIOIDS**

**HITTING THE PAIN AT ITS SOURCE**

# NEW COMPOUNDS (I)

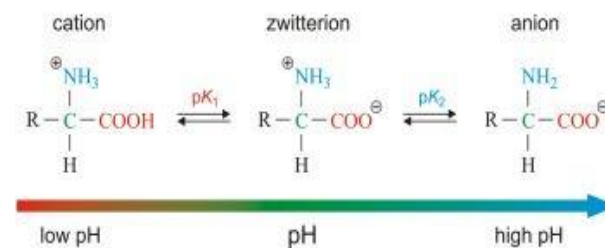


$\alpha$ -conjugates

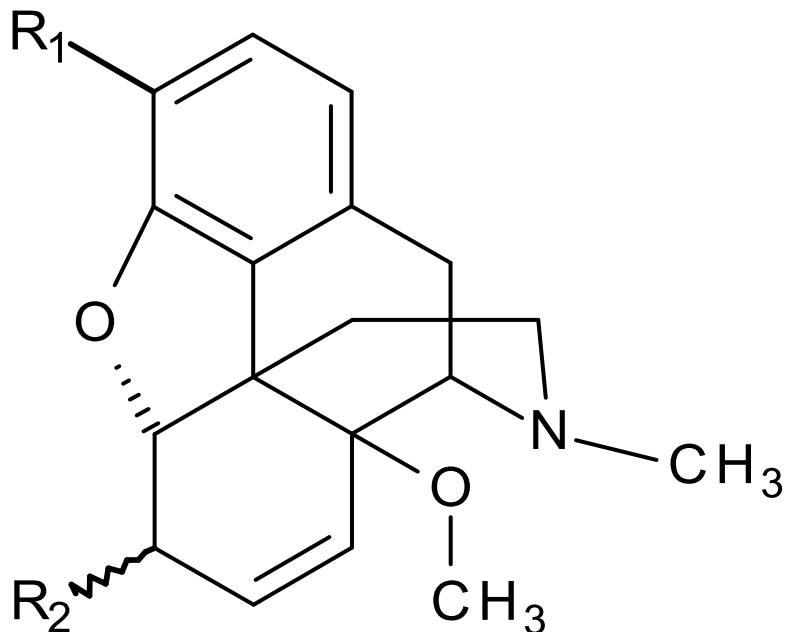


$\beta$ -conjugates

R	Compound
CH <sub>2</sub> COOH	HS-730 ( $\alpha$ ) HS-731 ( $\beta$ )
(S)-CH(CH <sub>3</sub> )COOH	HS-935 ( $\alpha$ ) HS-936 ( $\beta$ )
(S)-CH(CH <sub>2</sub> Ph)COOH	HS-937 ( $\alpha$ ) HS-938 ( $\beta$ )

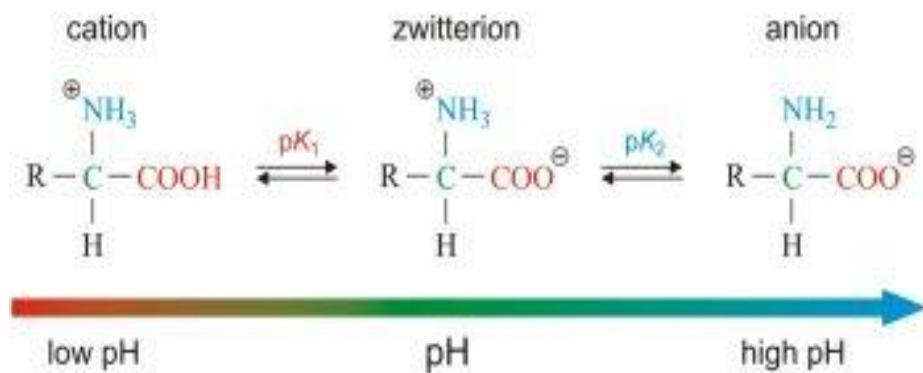


# NEW COMPOUNDS (II)



R1: OH

R2: OSO<sub>3</sub>



# Peripheral versus Central Antinociceptive Actions of 6-Amino Acid-Substituted Derivatives of 14-O-Methyloxymorphone in Acute and Inflammatory Pain in the Rat

Susanna Fürst, Pal Riba, Tamas Friedmann, Julia Tímar, Mahmoud Al-Khrasani, Ilona Obara, Wioletta Makuch, Mariana Spetea, Johannes Schütz, Ryszard Przewlocki, Barbara Przewlocka, and Helmut Schmidhammer

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Received July 28, 2004; accepted September 21, 2004

**Conclusion:** New opioids have limited access to the  
CNS and  
can mediate antinociception at peripheral sites

Research report

DAMGO and 6 $\beta$ -glycine substituted 14-*O*-methyloxymorphone but not morphine show peripheral, preemptive antinociception after systemic administration in a mouse visceral pain model and high intrinsic efficacy in the isolated rat vas deferens

Mahmoud Al-Khrasani<sup>a</sup>, Mariana Spetea<sup>b</sup>, Tamas Friedmann<sup>a</sup>, Pal Riba<sup>a</sup>,  
Kornel Király<sup>a</sup>, Helmut Schmidhammer<sup>b</sup>, Susanna Furst<sup>a,c,\*</sup>

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<sup>b</sup> *Department of Pharmaceutical Chemistry, Institute of Pharmacy and Center for Molecular Biosciences, University of Innsbruck, Innsbruck, Austria*

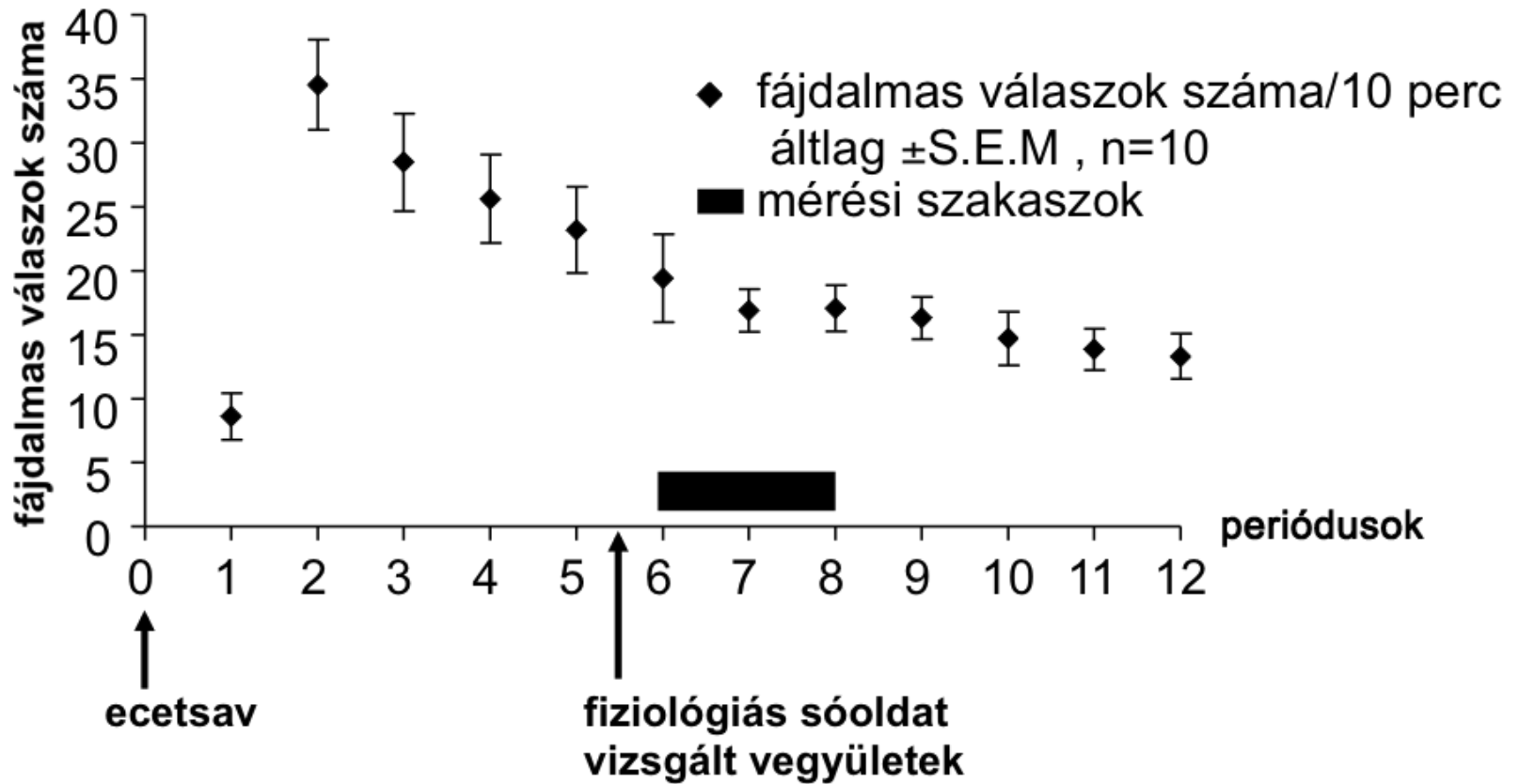
<sup>c</sup> *HAS-SE Group of Neuropsychopharmacology, Budapest, Hungary*

Received 2 June 2007; received in revised form 5 July 2007; accepted 5 July 2007

Available online 30 July 2007

**Conclusion:** New opioids have limited access to the  
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# RAT WRITHING TEST

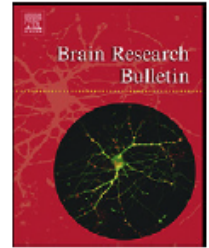




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## Brain Research Bulletin

journal homepage: [www.elsevier.com/locate/brainresbull](http://www.elsevier.com/locate/brainresbull)



Research report

### The central versus peripheral antinociceptive effects of $\mu$ -opioid receptor agonists in the new model of rat visceral pain

Mahmoud Al-Khrasani<sup>a,1</sup>, Erzsébet Lackó<sup>a,1</sup>, Pál Riba<sup>a</sup>, Kornél Király<sup>a</sup>, Melinda Sobor<sup>a,c</sup>, Júlia Timár<sup>a</sup>, Shaaban Mousa<sup>b</sup>, Michael Schäfer<sup>b</sup>, Susanna Füst<sup>a,\*</sup>

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<sup>b</sup> Department of Anaesthesiology and Intensive Care Medicine, Charité University Berlin, Campus Virchow Klinikum and Campus Charite Mitte, Berlin, Germany

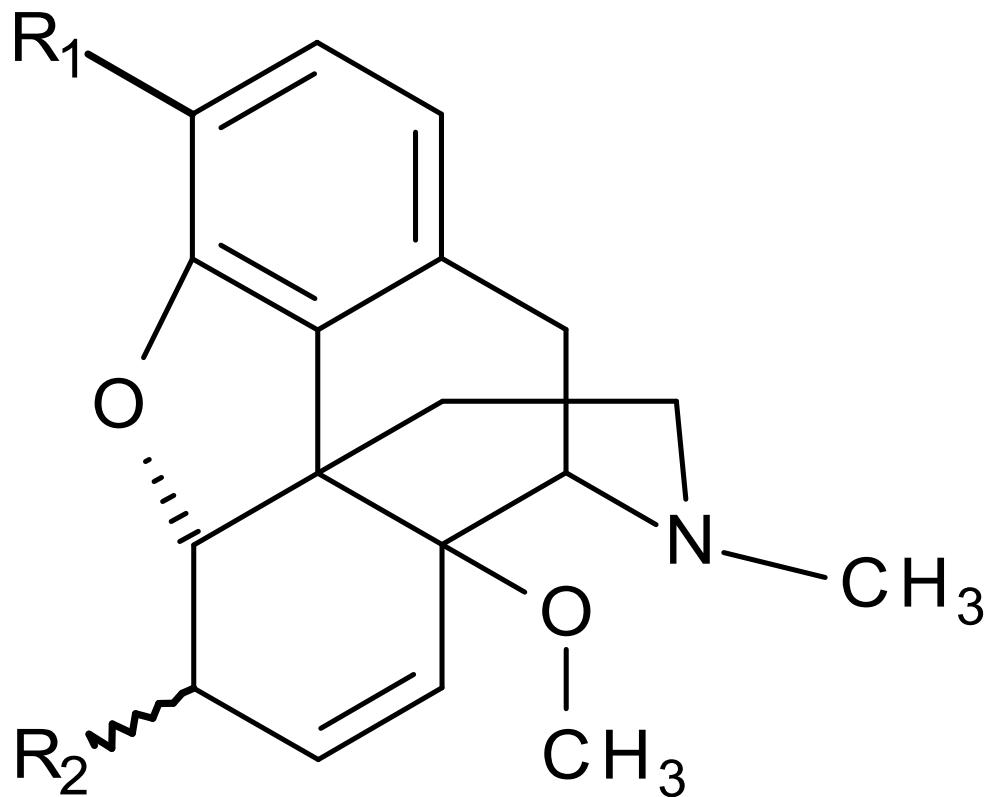
<sup>c</sup> National Institute for Quality and Organizational Development of Healthcare and Medicine, Diós árok 3, H-1125 Budapest, Hungary

## Conclusion:

- in the rat late permanent visceral pain model
- systemic morphine has prominent central antinociceptive effects.
- systemic DAMGO shows peripheral effect.
- this model closely resembles the clinical situation.



# NEW COMPOUNDS (II)



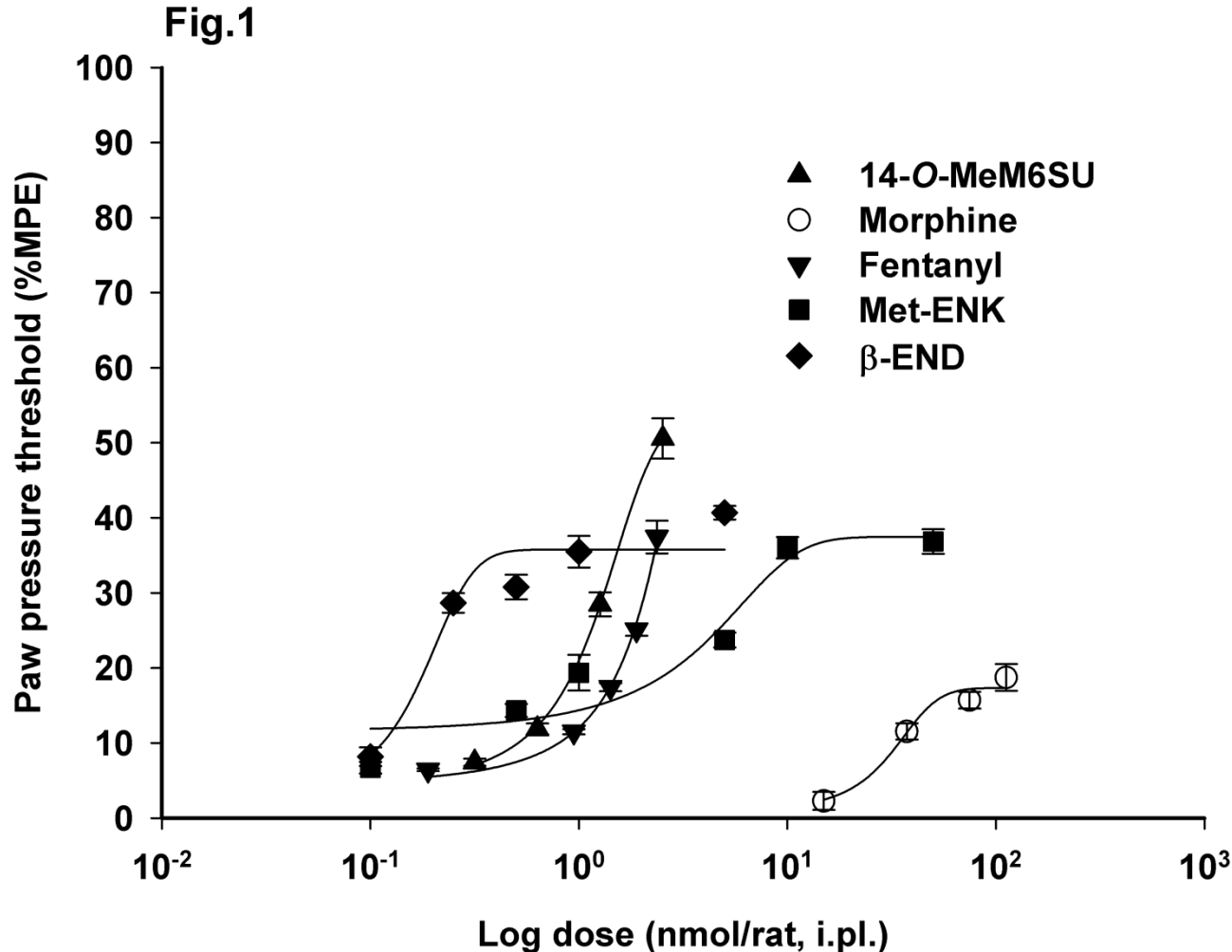
**A novel  $\mu$ -opioid receptor ligand with high in vitro and in vivo agonist efficacy.**

Lacko E<sup>1</sup>, Varadi A, Rapavi R, Zador F, Riba P, Benyhe S, Borsodi A, Hosztafi S, Timar J, Noszal B, Furst S, Al-Khrasani M.

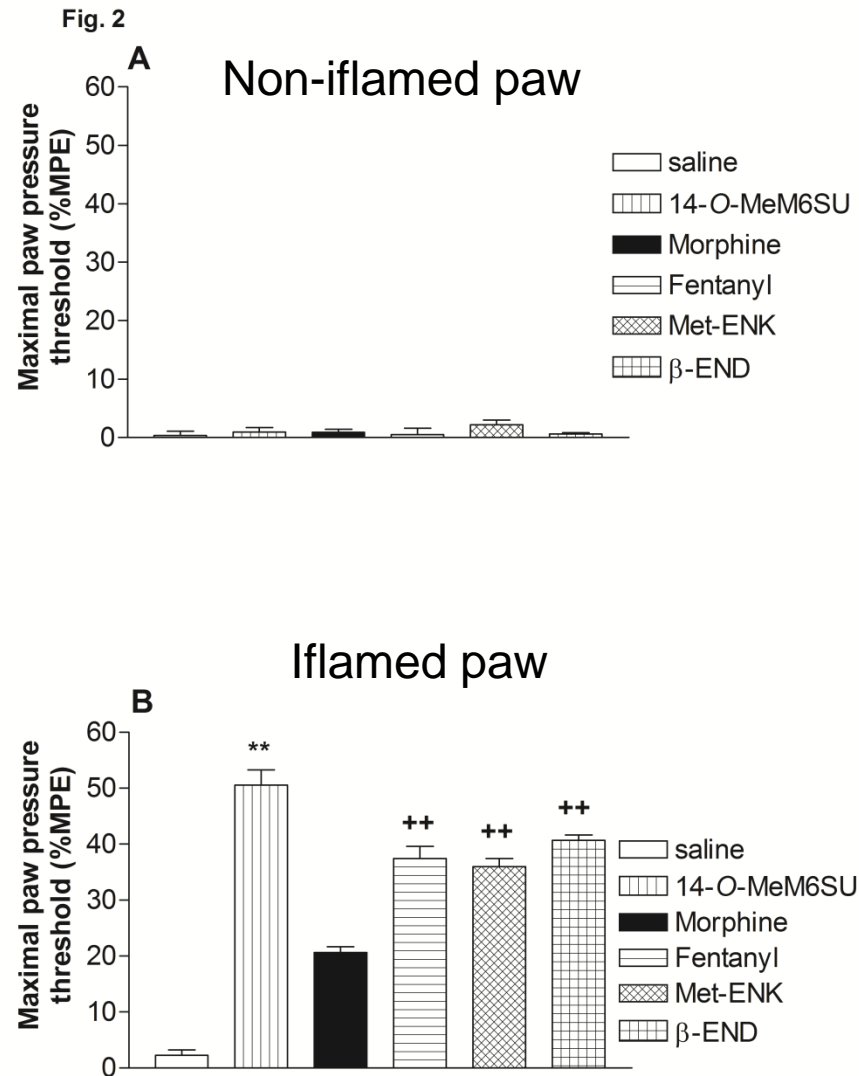
Curr Med Chem. 2012;19(27):4699-707.

# RESULT OBTAINED FROM FCA-INDUCED PAIN

Dose–response relationships for opioid agonists at 5 min after injection into inflamed paw.



# The local maximal possible antinociceptive effects.





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### Neuropharmacology and analgesia

Peripheral antinociceptive efficacy and potency of a novel opioid compound 14-*O*-MeM6SU in comparison to known peptide and non-peptide opioid agonists in a rat model of inflammatory pain

Baled. I. Khalefa<sup>b</sup>, Shaaban A. Mousa<sup>b</sup>, Mohammed Shaqura<sup>b</sup>, Erzsébet Lackó<sup>a</sup>, Sándor Hosztafi<sup>c</sup>, Pál Riba<sup>a</sup>, Michael Schäfer<sup>b</sup>, Péter Ferdinandy<sup>a</sup>, Susanna Fürst<sup>a</sup>, Mahmoud Al-Khrasani<sup>a,\*</sup>

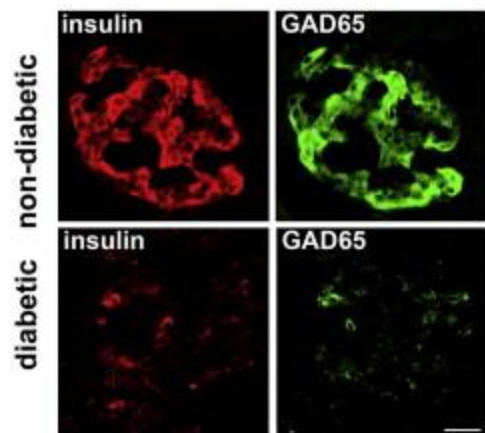
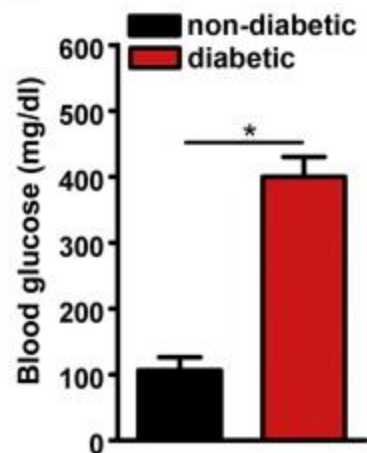
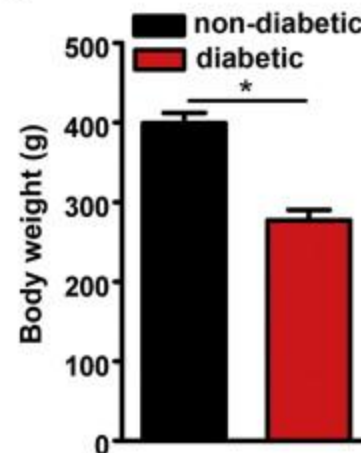
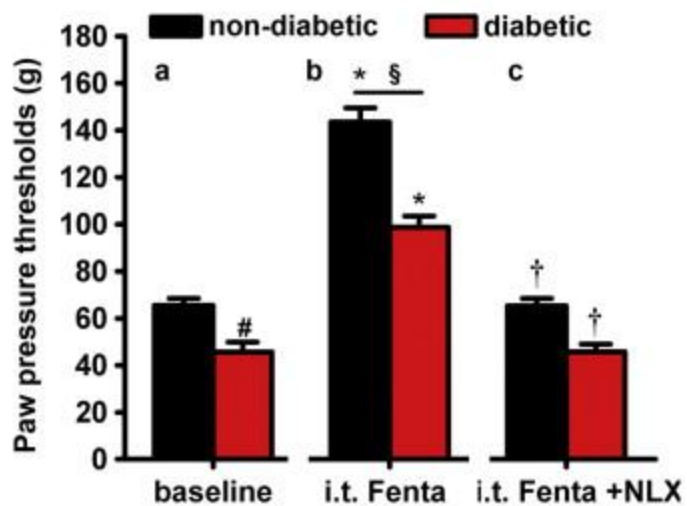
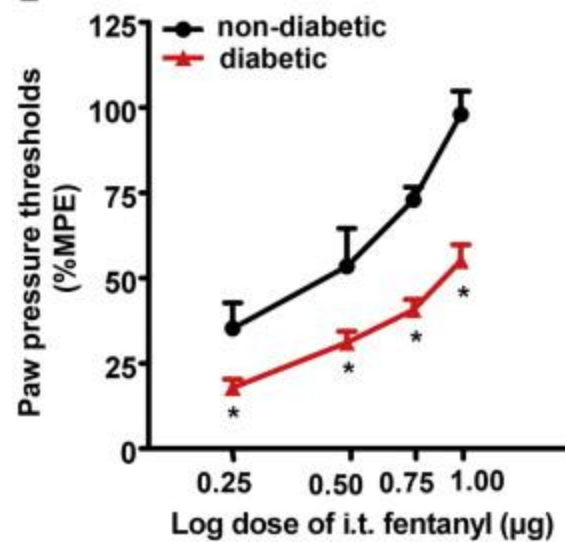
<sup>a</sup> Department of Pharmacology and Pharmacotherapy, Faculty of Medicine, Semmelweis University, Nagyvárad tér 4, P.O. Box 370, H-1445 Budapest, Hungary

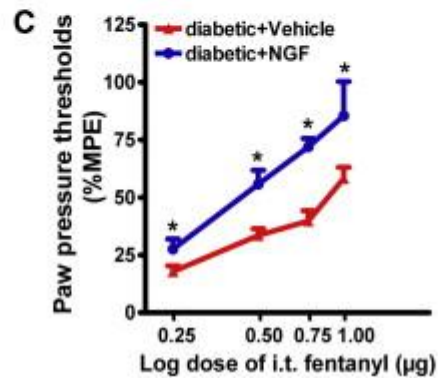
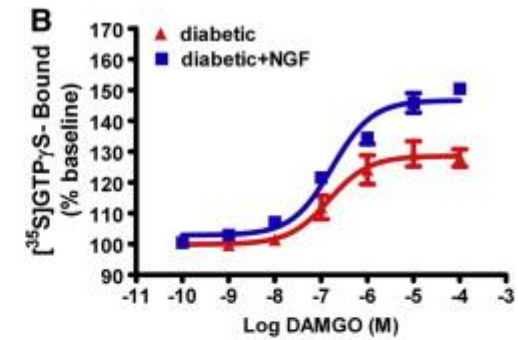
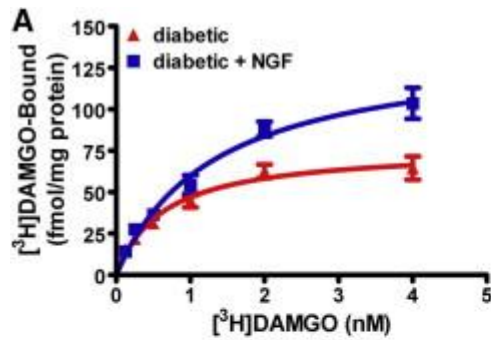
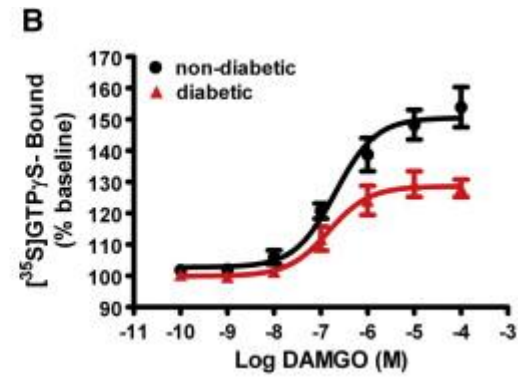
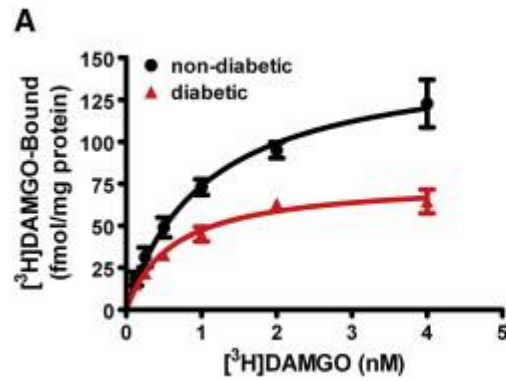
<sup>b</sup> Department of Anesthesiology and Intensive Care Medicine, Charité University Berlin, Campus Virchow Klinikum and Campus Charite Mitte, Augustenburgerplatz 113353 Berlin, Germany

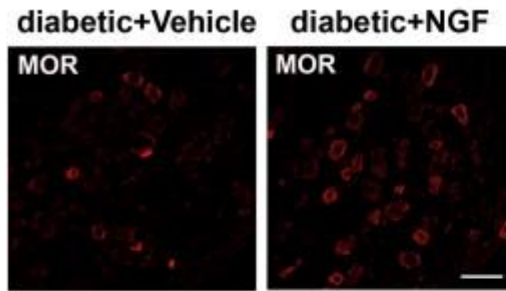
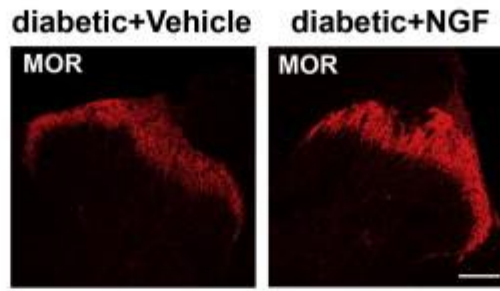
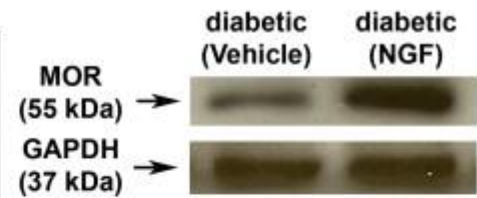
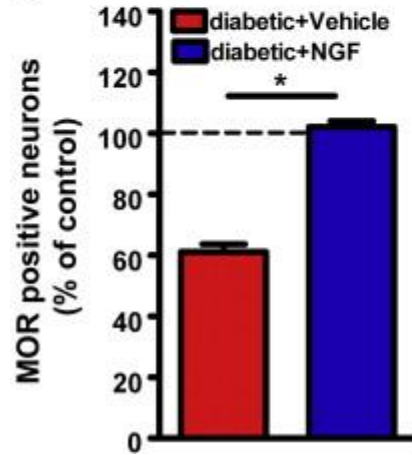
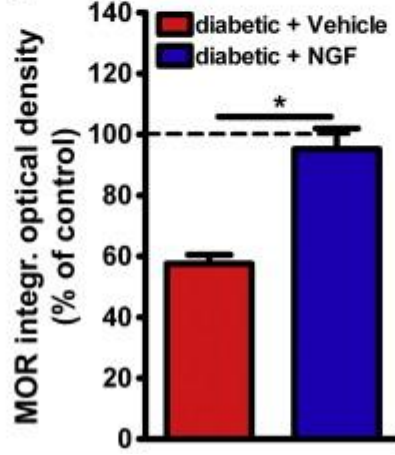
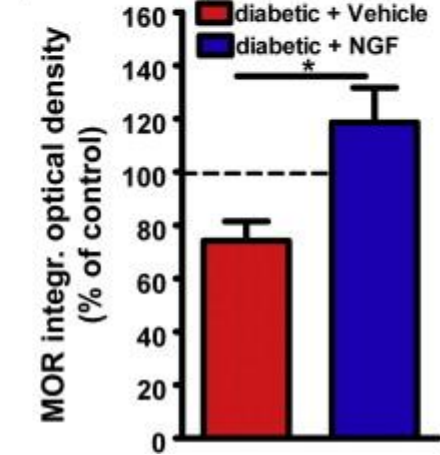
<sup>c</sup> Department of Pharmaceutical Chemistry, Semmelweis University, Hógyes Endre u., 9. H-1092 Budapest, Hungary



**Conclusion:** The observed superiority of local antinociceptive effects of 14-*O*-MeM6SU in comparison to non-peptide and peptide opioid agonists might be due to both pharmacodynamic (the efficacy, the receptor reserve and the selectivity) and pharmacokinetic parameters.

**A****B****C****D****E**



**A****C****E****B****D****F**

## Reduced Number, G Protein Coupling, and Antinociceptive Efficacy of Spinal Mu-Opioid Receptors in Diabetic Rats Are Reversed by Nerve Growth Factor

Mohammed Shaqura,<sup>\*</sup> Baled I. Khalefa,<sup>\*</sup> Mehdi Shakibaei,<sup>†</sup> Jens Winkler,<sup>\*</sup> Mahmoud Al-Khrasani,<sup>‡</sup> Susanna Fürst,<sup>‡</sup> Shaaban A. Mousa,<sup>\*</sup> and Michael Schäfer<sup>\*</sup>

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<sup>†</sup>*Department of Anatomy, Ludwig-Maximilian-University Munich, Germany.*

<sup>‡</sup>*Department of Pharmacology and Pharmacotherapy, Semmelweis University, Budapest, Hungary.*

For the first time we show a loss in MOR-IR neurons, membrane-spanning receptors, and functional G protein coupling during advanced STZ-induced diabetes as a contributing factor for the impaired antinociception of i.t.-delivered MOR opioid agonists.

Pretreatment with i.t. NGF reversed these alterations and rescued opioid responsiveness.