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

AL-KHRASANI MAHMOUD

al-khrasani.mahmoud@med.semmelweis-univ.hu

Semmelweis Egyetem
Farmakológiai és Farmakoterápiás Intézet

2016

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

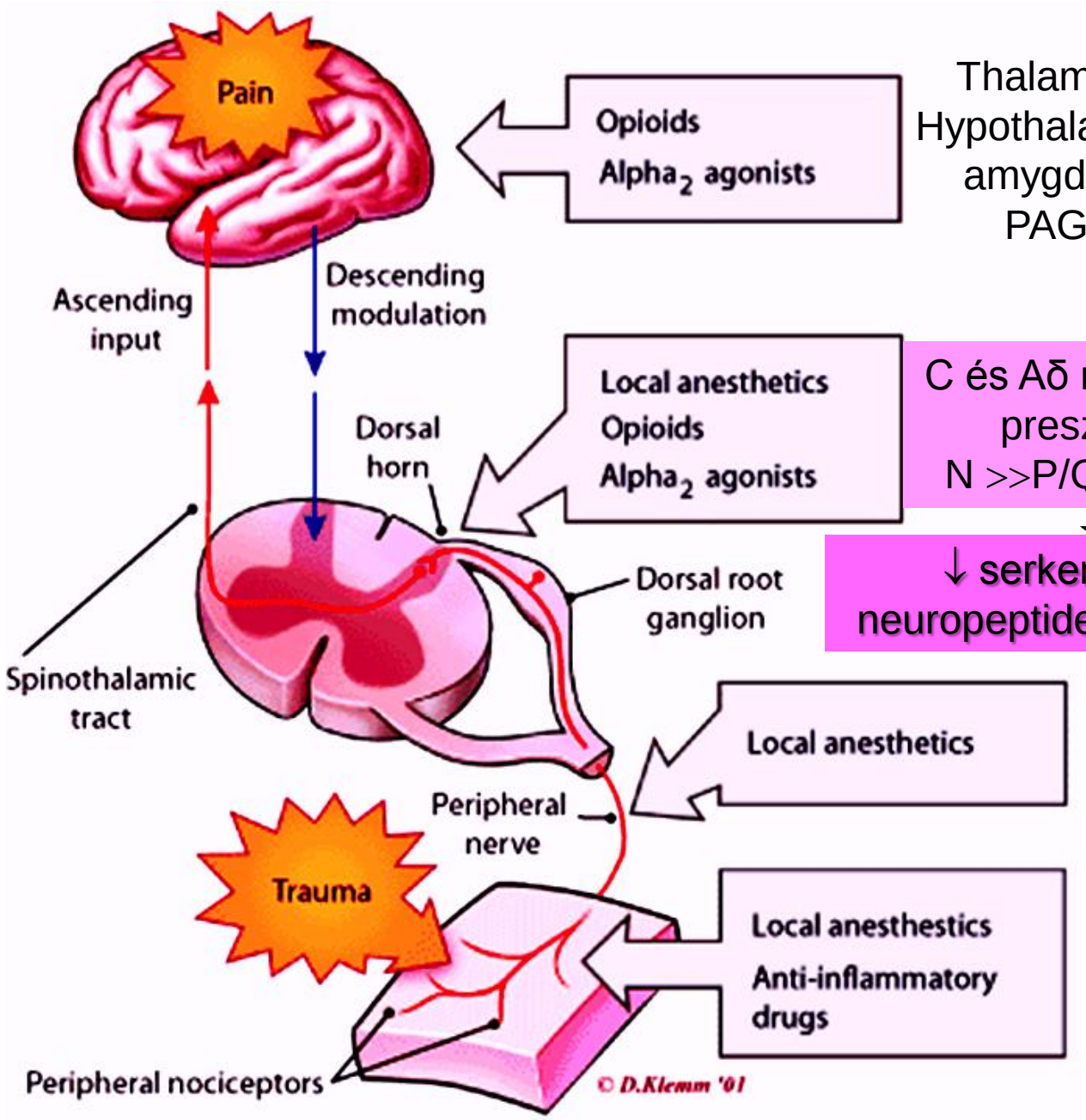
many ways to classify pain

Nociceptive
Somatic
Visceral

Inflammatory
evoked by proinflammatory m.
Many
acid
activation & sensitization of
nociceptive pain pathway

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)

THE TARGETS OF ANALGESIC AGENTS



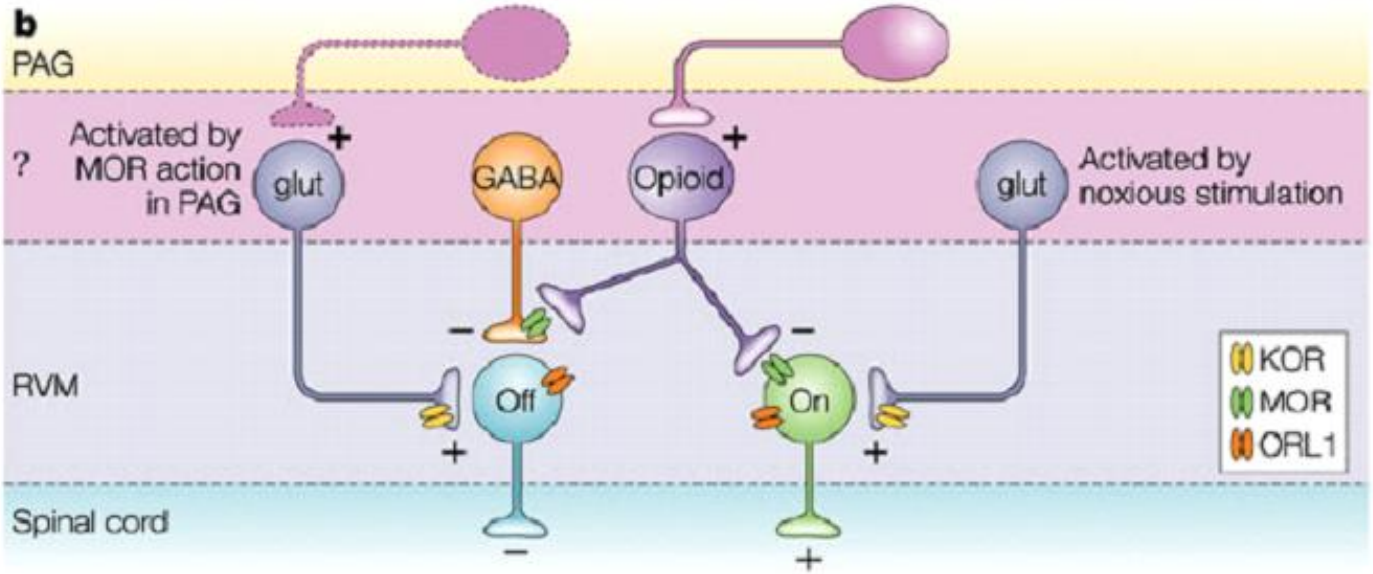
Thalamus
Hypothalamus
amygdala
PAG

C és Aδ rostok (MOR)
preszinaptikus
N >>P/Q Ca^{2+} gátlás

↓ serkentő neurohormonok
neuropeptidek (glutamát & P-anyag)

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 Aδ and C fibers.

On the peripheral terminals partially indentified mechanisms taking up the stimulus

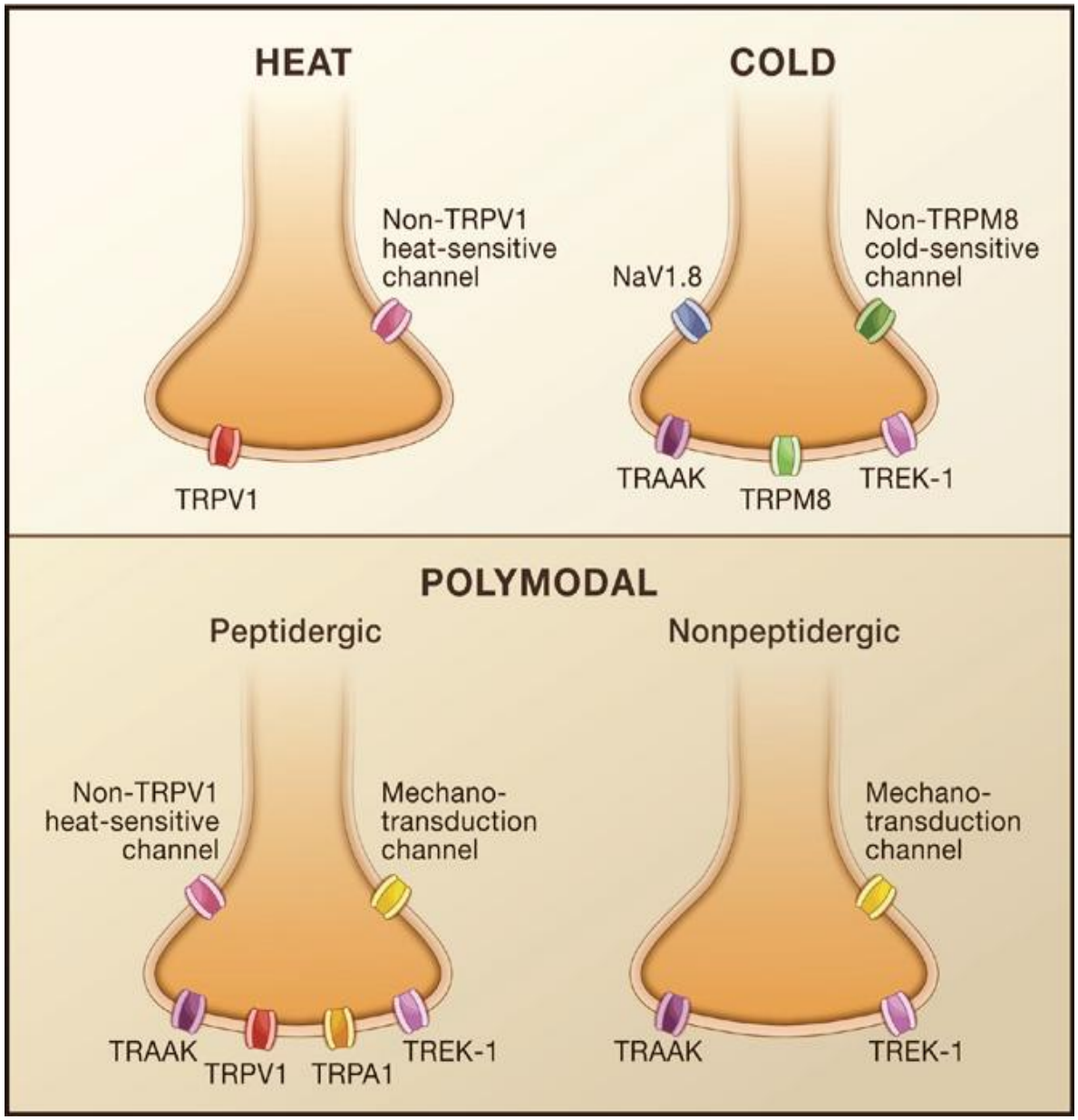
- TRPV1 (capsaicin sense): heat and low pH
- TRPV2: heat
- ASICS channels: low pH
- TRPM8 (menthol): cold
- TRPA: chemical irritants (acids)
- Transient receptor potential ankyrin 1 mustard oil
- ENaC (Epithelial Na chanel): mechanical stim.
- Mechanosensitive K channels (KCKN family: TREK and TRAAK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

PRIMARY AFFERENT FIBRES

- Noxious sensory information carrier:
  Aδ and C fibers
- Non-noxious stimulus carrier: Aβ fibers

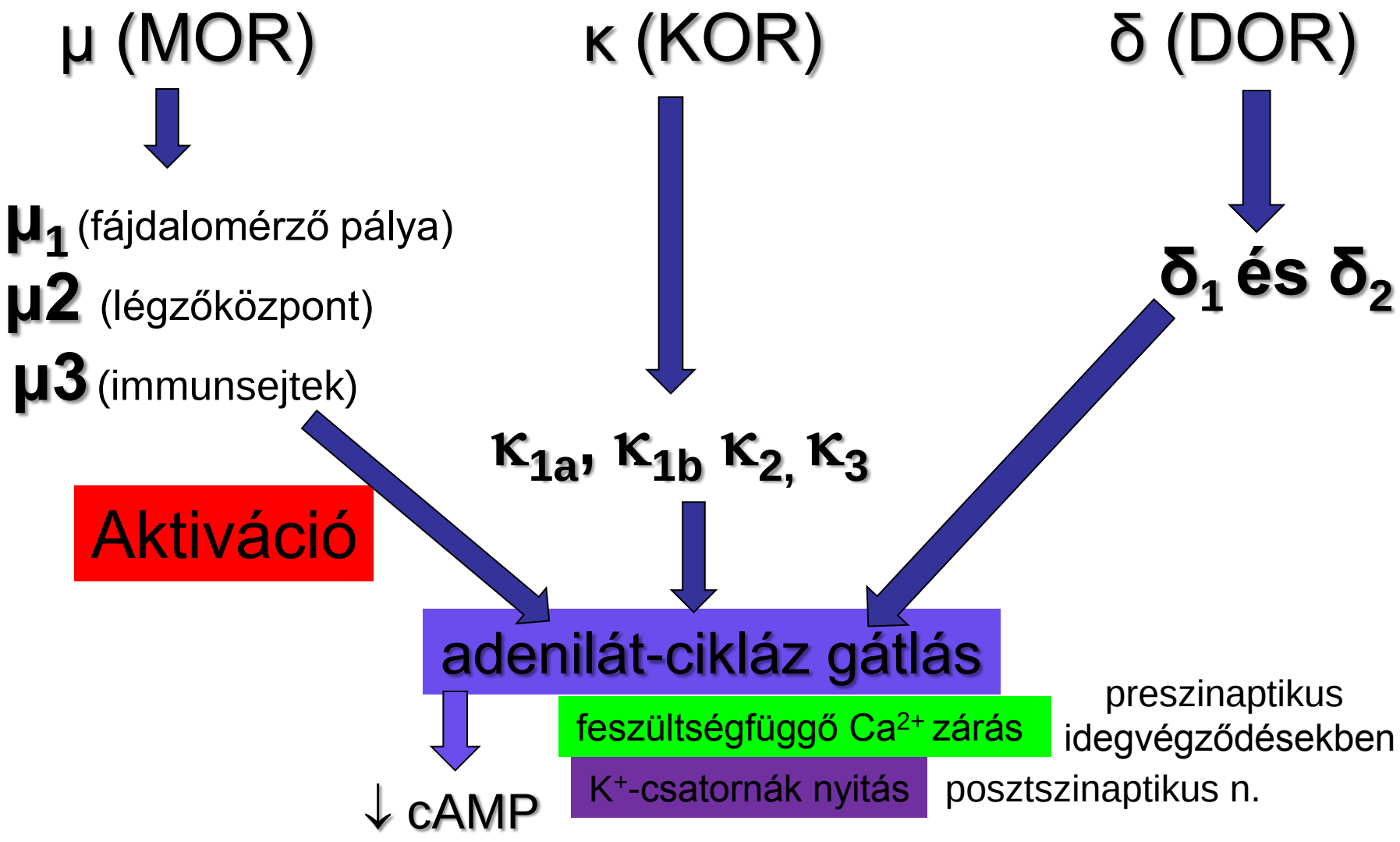
	Aβ	**Aδ**	**C**
Diameter	Large	Small 2-5μm	Smallest <2μm
Myelination	Highly	Thinly	Unmyelinated
Conduction velocity	> 40 ms-1	5-15ms-1	< 2ms-1
Receptor activation thresholds	Low	High and low	High
Sensation on stimulation	Light touch, non-noxious	Rapid, sharp, localised pain	Slow, diffuse, dull Burning pain
		Mechanical and thermal stimuli responsible for the initial reflex response to acute pain	Polymodal

Polymodal: responding to multiple modalities, chemical, mechanical (touch, pressure, stretch) and thermal stimuli

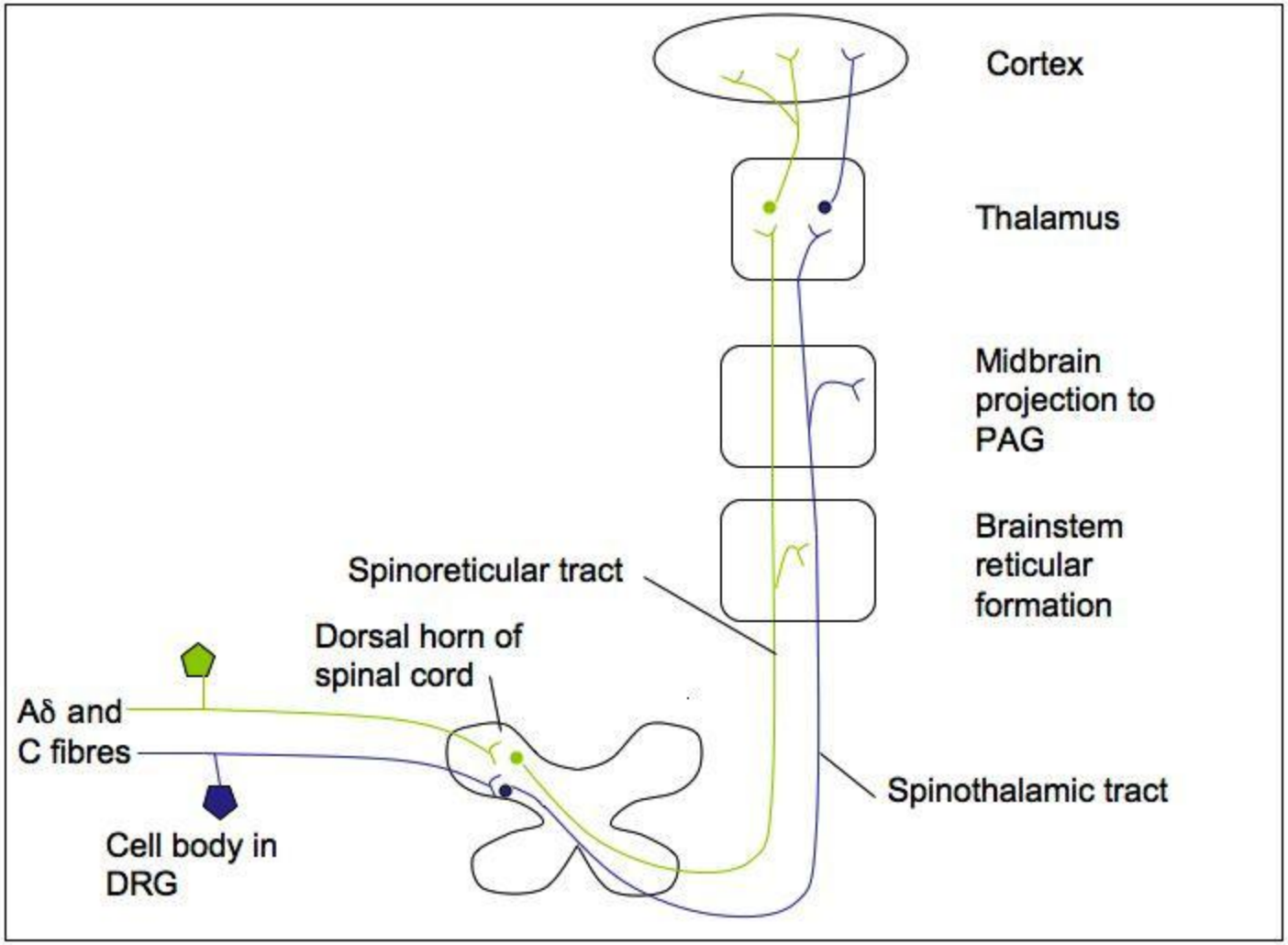

HEAT
Non-TRPV1
heat-sensitive
channel
TRPV1
COLD
NaV1.8
Non-TRPM8
cold-sensitive
channel
TRAAK
TRPM8
TREK-1
POLYMODAL
Peptidergic
Non-TRPV1
heat-sensitive
channel
Mechano-
transduction
channel
TRAAK
TRPV1
TRPA1
TREK-1
Nonpeptidergic
Mechano-
transduction
channel
TRAAK
TREK-1

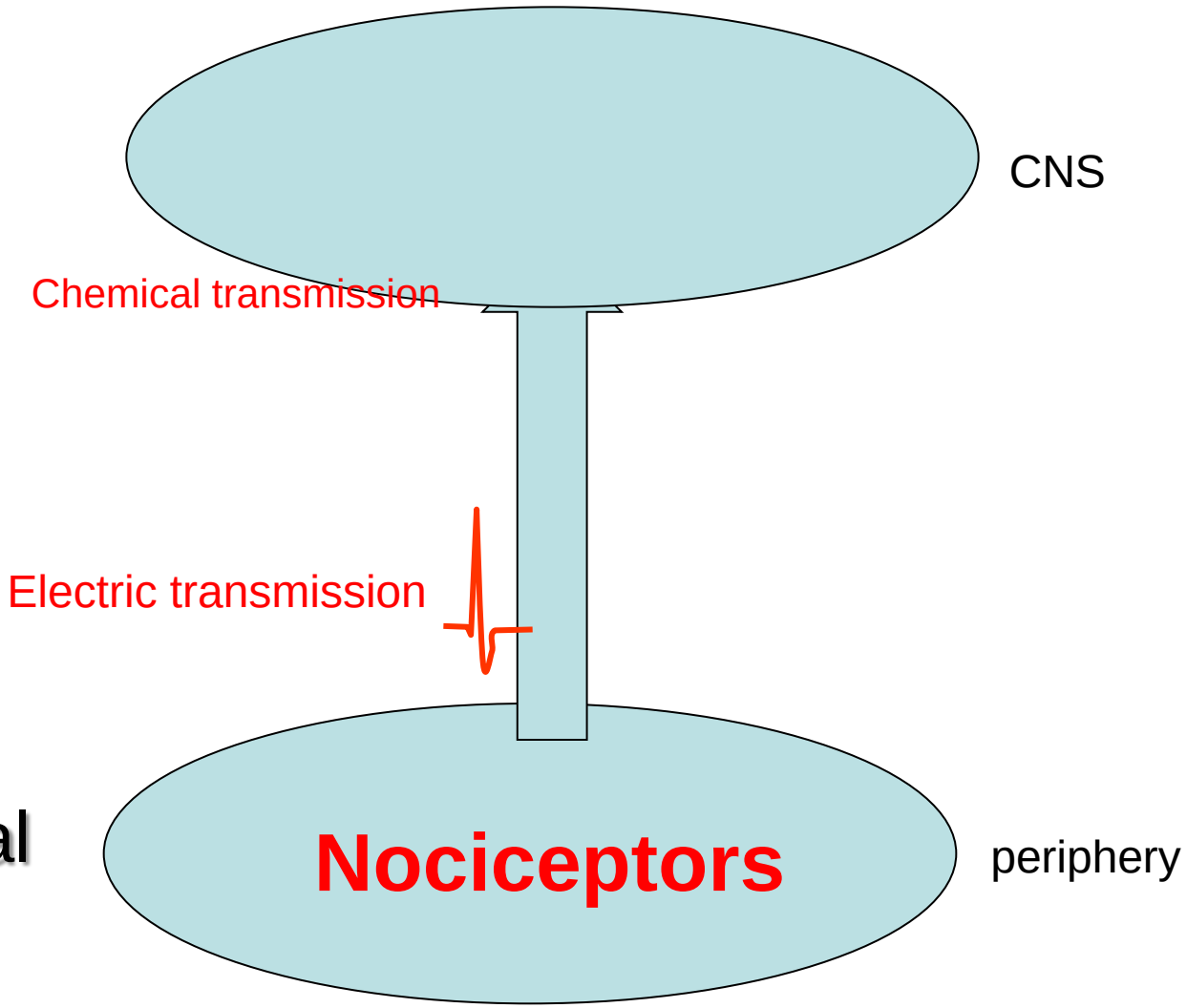
OPIOID RECEPTOROK

G-protein-kapcsolt



Ascending pain pathways





Stimuli
Mechanical
thermal
chemical

free nerve endings of primary afferent Aδ and C fibres

TISSUE DAMAGE

↓

RELEASE INFLAMMATORY MEDIATORS

Bradykinin
serotonin
prostaglandins
Cytokines
H+

↓ threshold

↓

Less stimuli

primary sensitisation

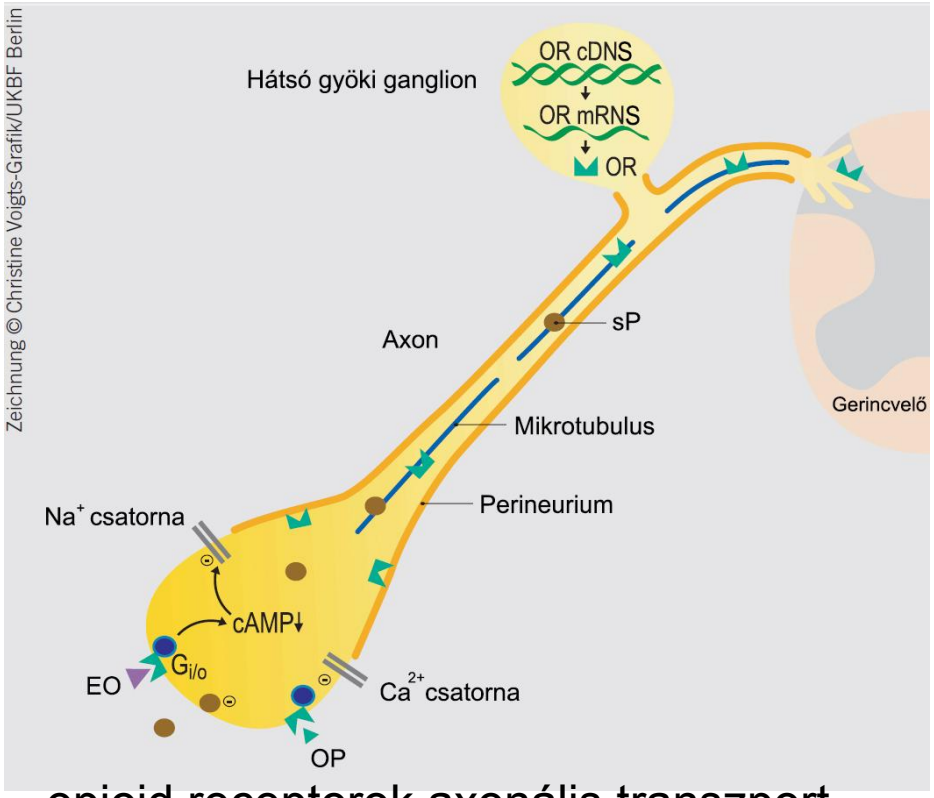
↓

nociceptors stimulation

PERIFÉRIÁS OPIOID RECEPTOROK

Immunsejtek

Centrális & perifériás elsődleges érző n. hátsógyöki ganglion



opioid 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^+, K^+ and Ca^{2+} channels

transient receptor potential vanilloid 1 (TRPV1)

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

-Tetrodotoxin-resistant (TTX-R) Na^+ 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+ 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)

- $Ca_v\alpha2\delta$-1 channel subunit
- Na_v1.3 sodium channel (1nM TTX)
- Bradykinin (BK) B1 and capsaicin TRPV1 receptors

Down regulation of the following:

- Na_v1.8 Na channel (100μM TTX)
- B2 receptor, substance P (SP), MORs in unmyelinated ns.

PERIFÉRIÁS OPIOID RECEPTOROK

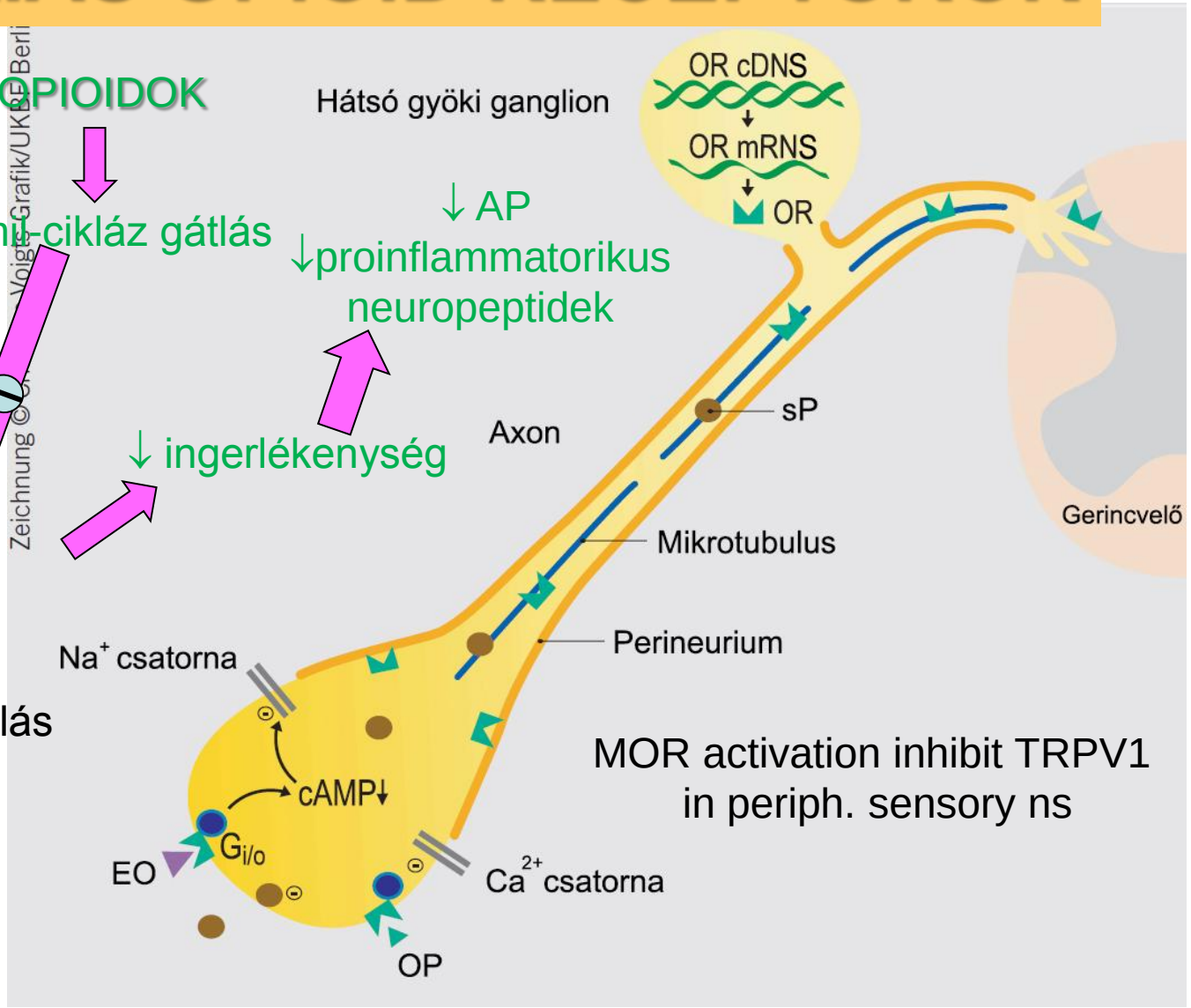
szenzitizált nociceptorok

sérült idegek

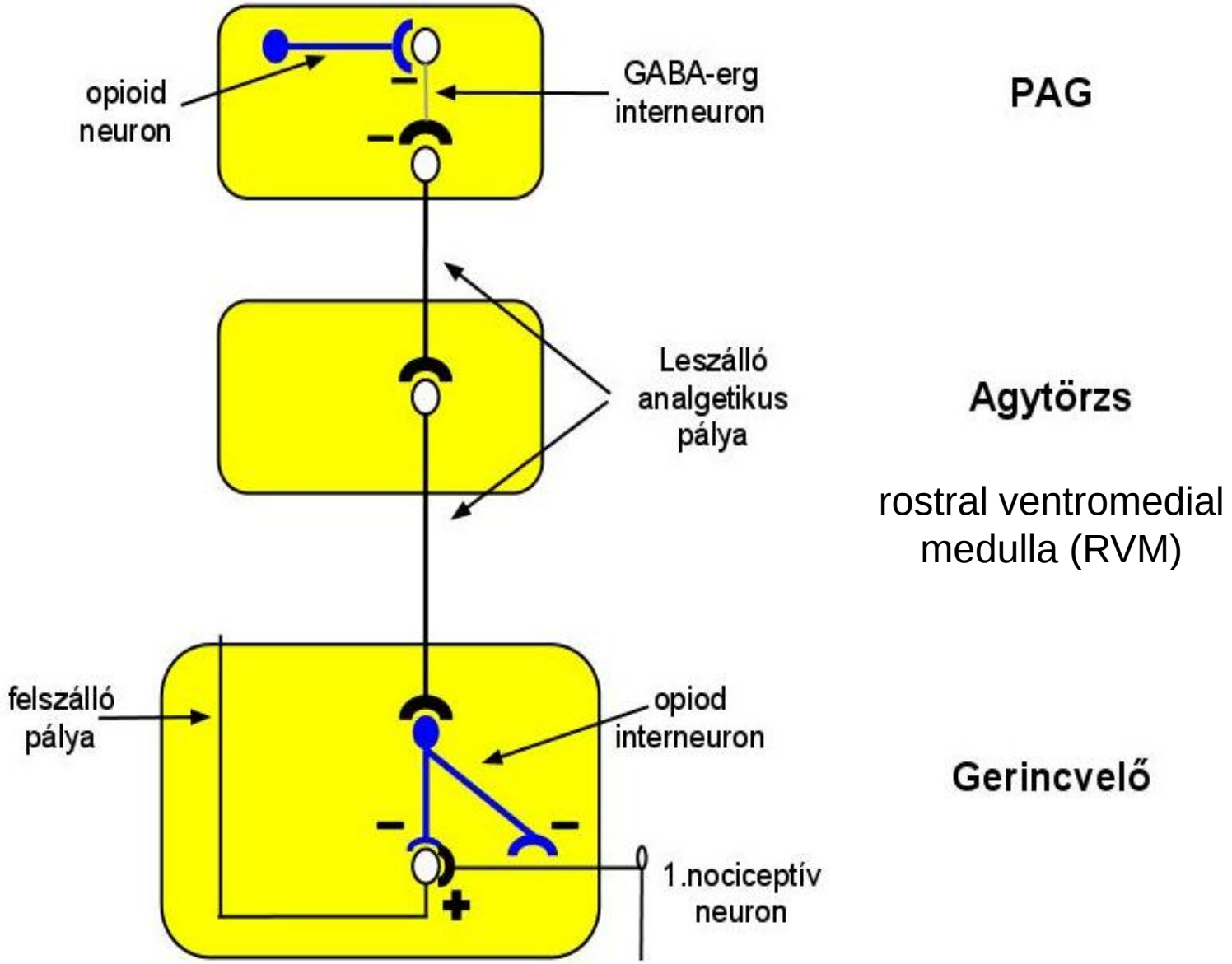
tetrodotoxin Na^+ csat.

fájdalomimpulzus kialakulás

spontán aktivitás



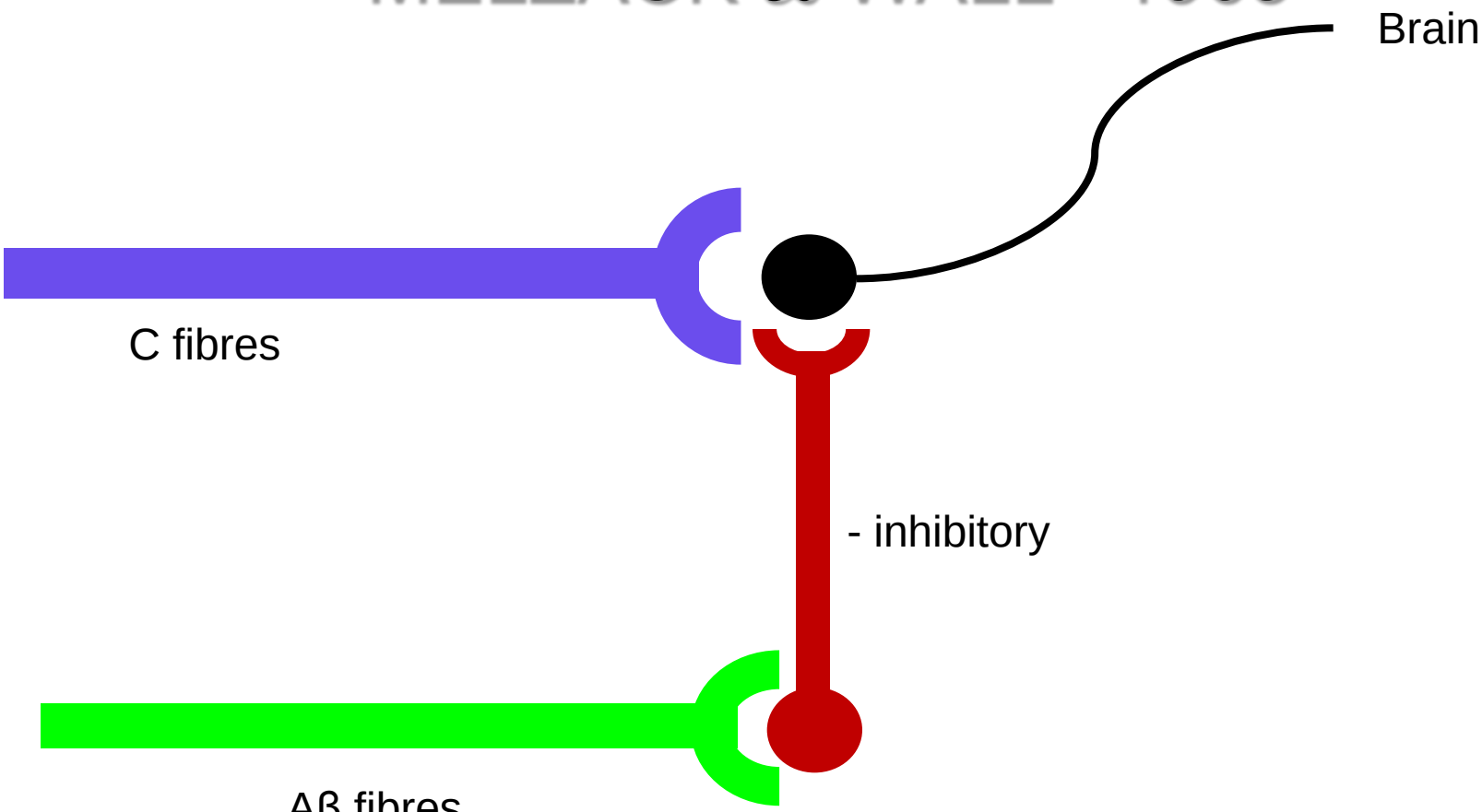
OR: capsaicin receptorral rendelkező viscerális rostokon
P-anyagot, CGRP-et és izolektin B4-et szintetizáló n. (Borgland 2001).



Descending inhibitory modulation: periaqueductal grey (PAG); rostral ventromedial medulla (RVM)

GATE CONTROL THEORY OF PAIN

MELZACK & WALL 1965



non-painful input closes the "gates" to painful input

ANIMAL PAIN MODELS

PAIN INDUCERS

- THERMAL

To demonestrate the effect of opioids on acute or chronic pain.

- CHEMICALS

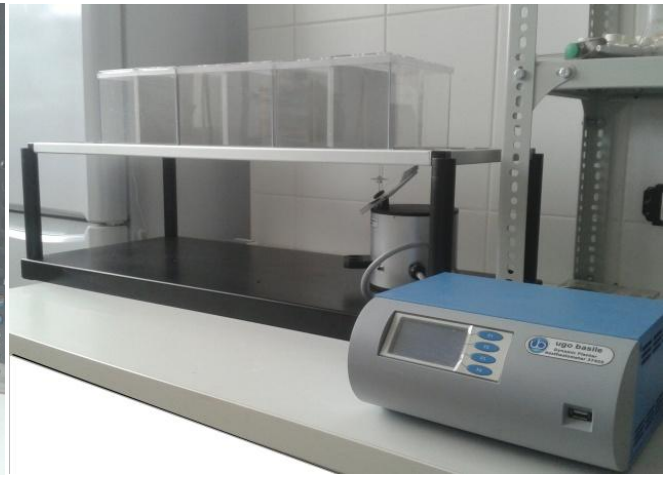
For acute or chronic pain.

- DIRECT NEURONAL DAMAGES

For chronic pain.

ANIMAL PAIN MODELS

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



FCA or CFA: Freund's complete adjuvant

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

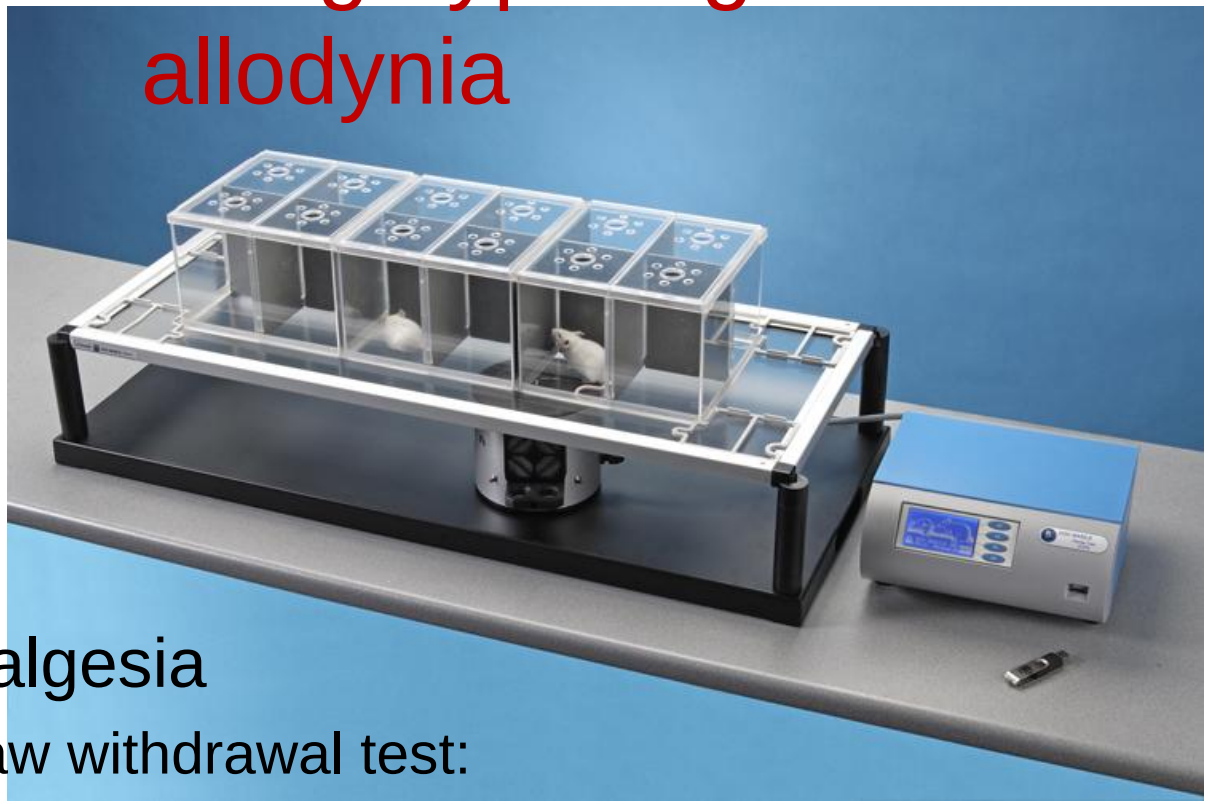
  It is a more complicated reflex

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 pain
  - Tail pinch test: the tail is put between a plate and a cogwheel (fogaskerekű) like structure and it sets increasing force on it – used sgt. For testing κ 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

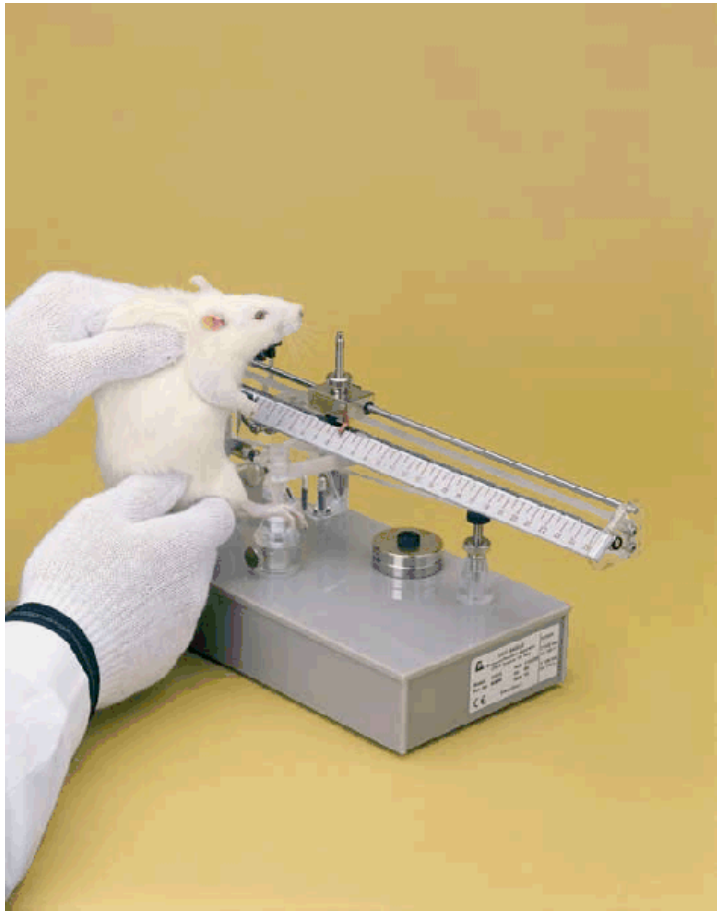
Test methods for hyperalgesia and allodynia

- 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.

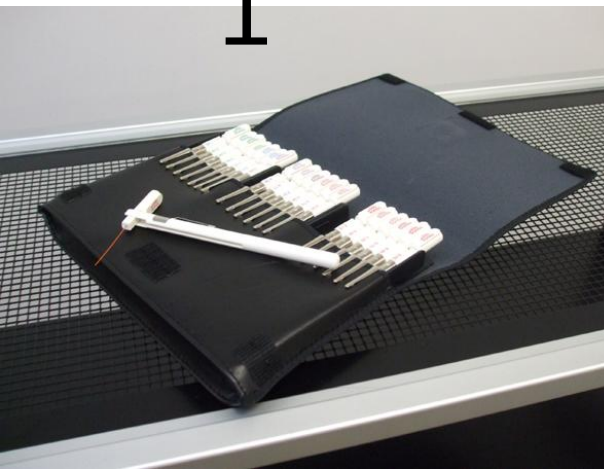
1- Classic

2- Electronic

3- Automatic: Dynamic Plantar Aesthesiometer (DPA)

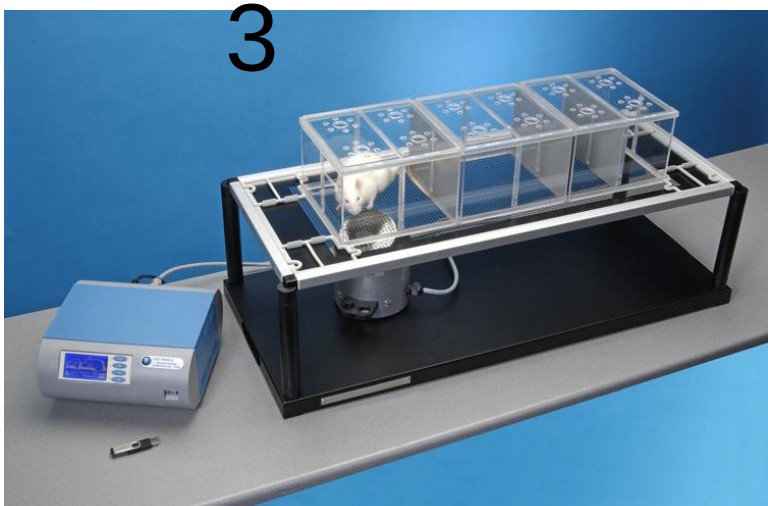
– Sham or contralateral paws are used as control

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.

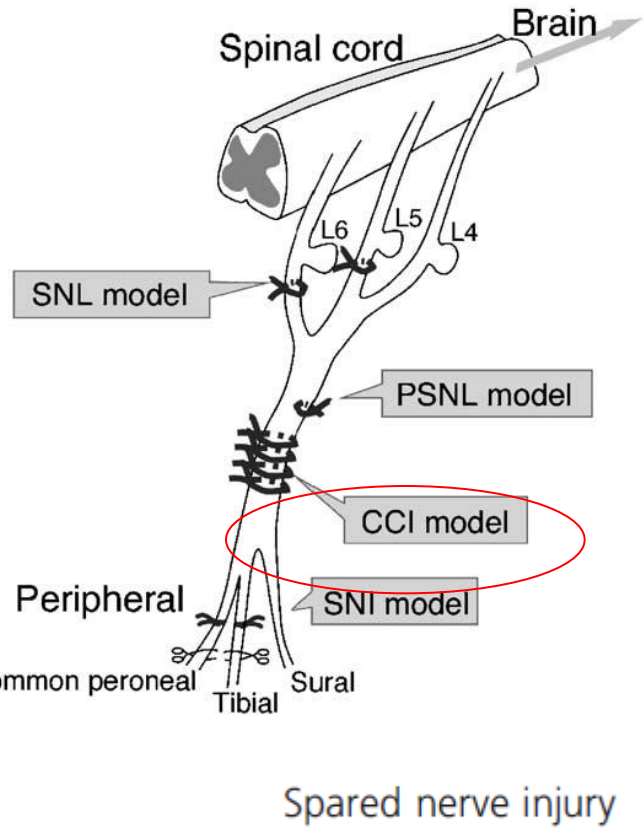
INFLAMMATORY PAIN MODELS

- 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 spontaneus 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

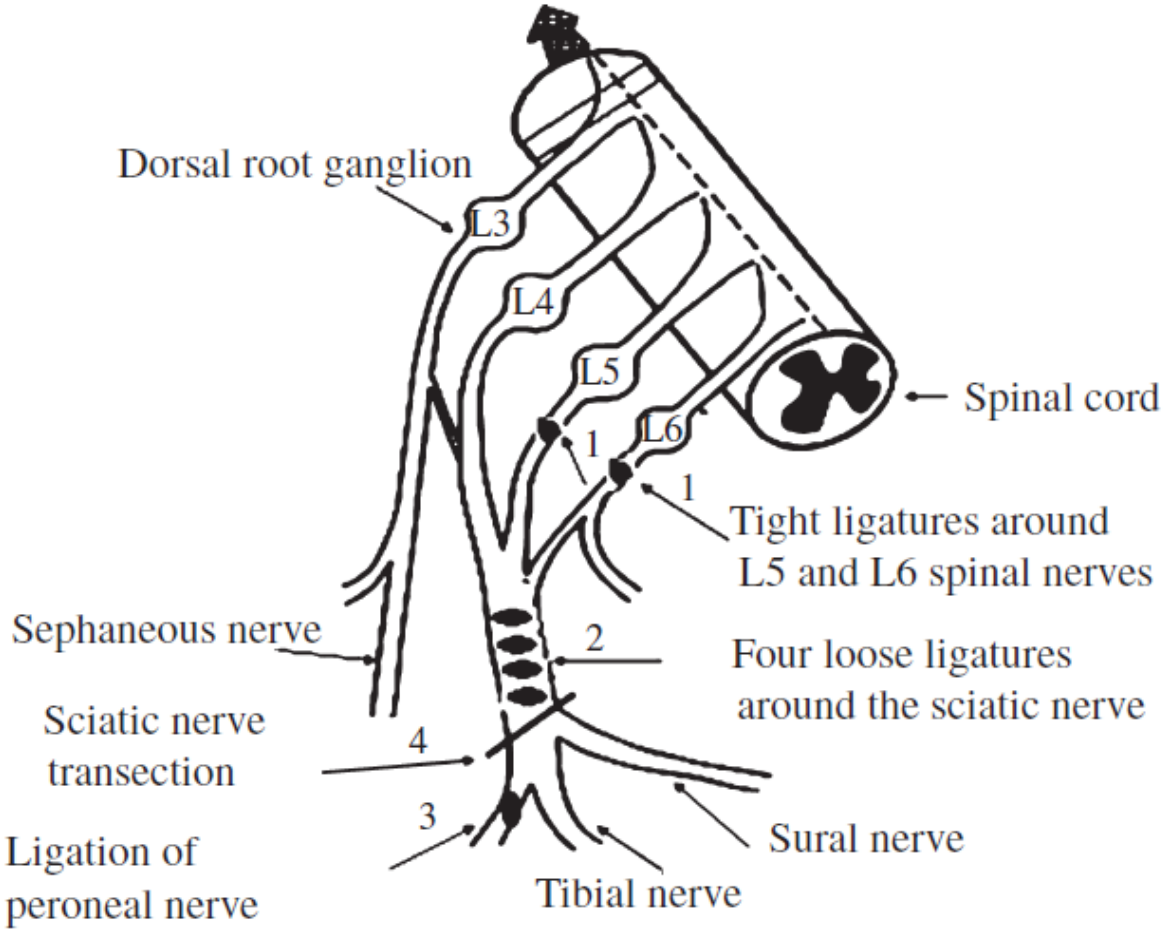


Partial sciatic nerve ligation (PSL/Seltzer model), Pain (1990) 43 205–218.

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

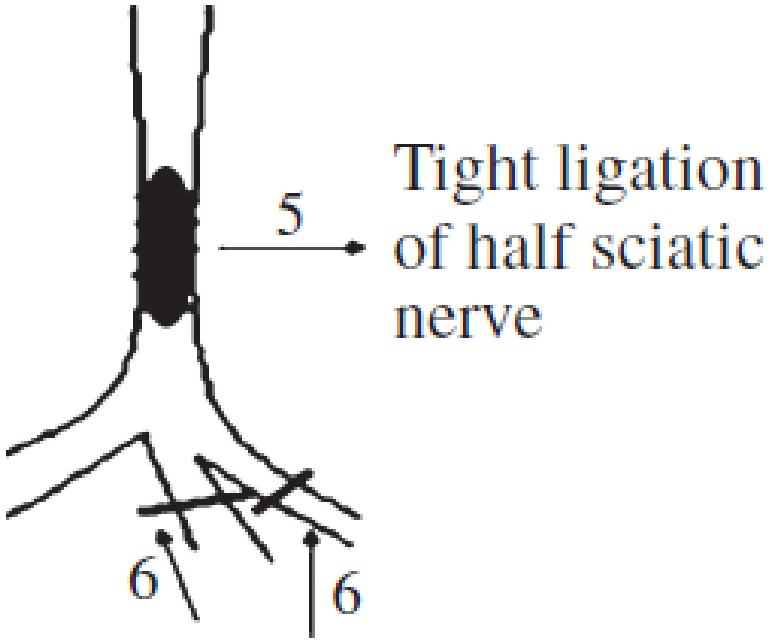


Table I List of different animal models of neuropathic pain.

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, *Macaca fascicularis*
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

Amteshwar et al., 2011

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		

Amteshwar et al., 2011

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

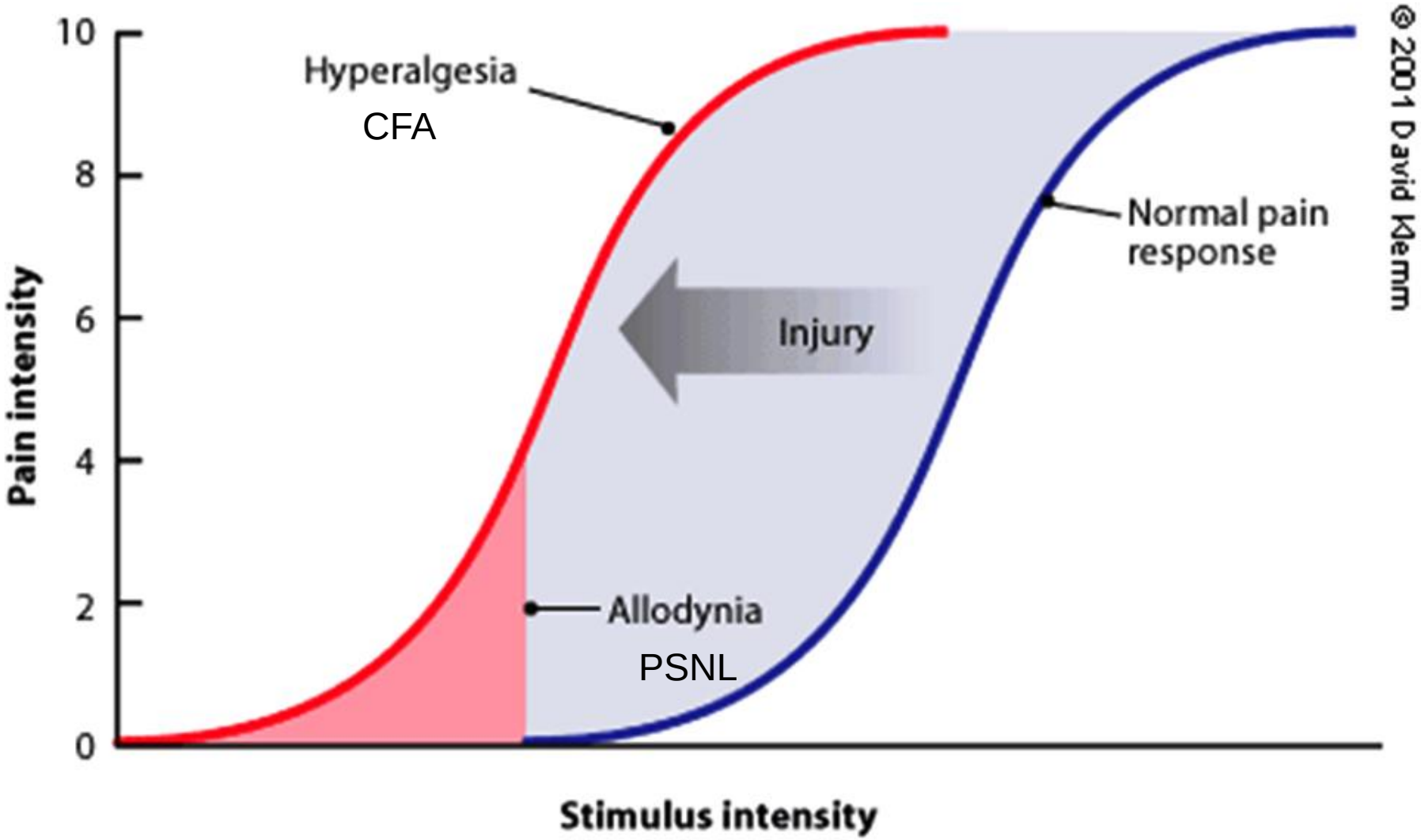
Amteshwar et al., 2011

PAIN TYPES

Types	Source	Innervation	Character.
Visceral	internal organs	C fibres	diffuse and poorly localised, (deep, dull or dragging)
Neuropathic	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.

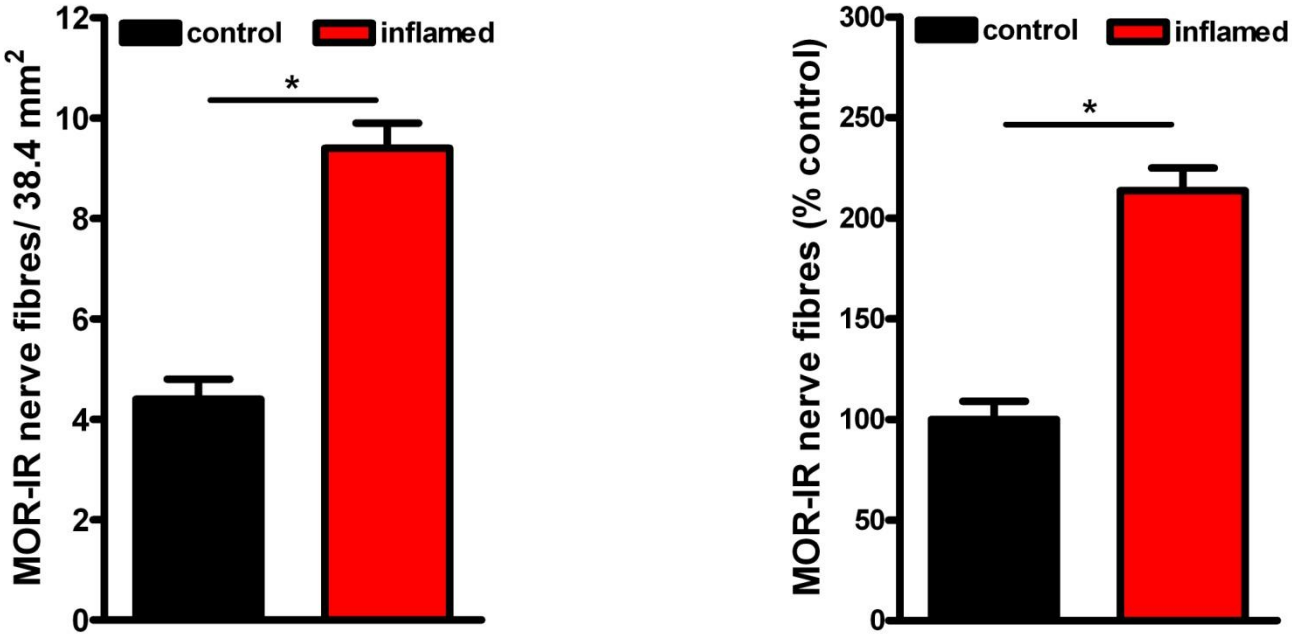
Hyperalgesia: pain may be a heightened response to a stimulus that is usually painful.



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.

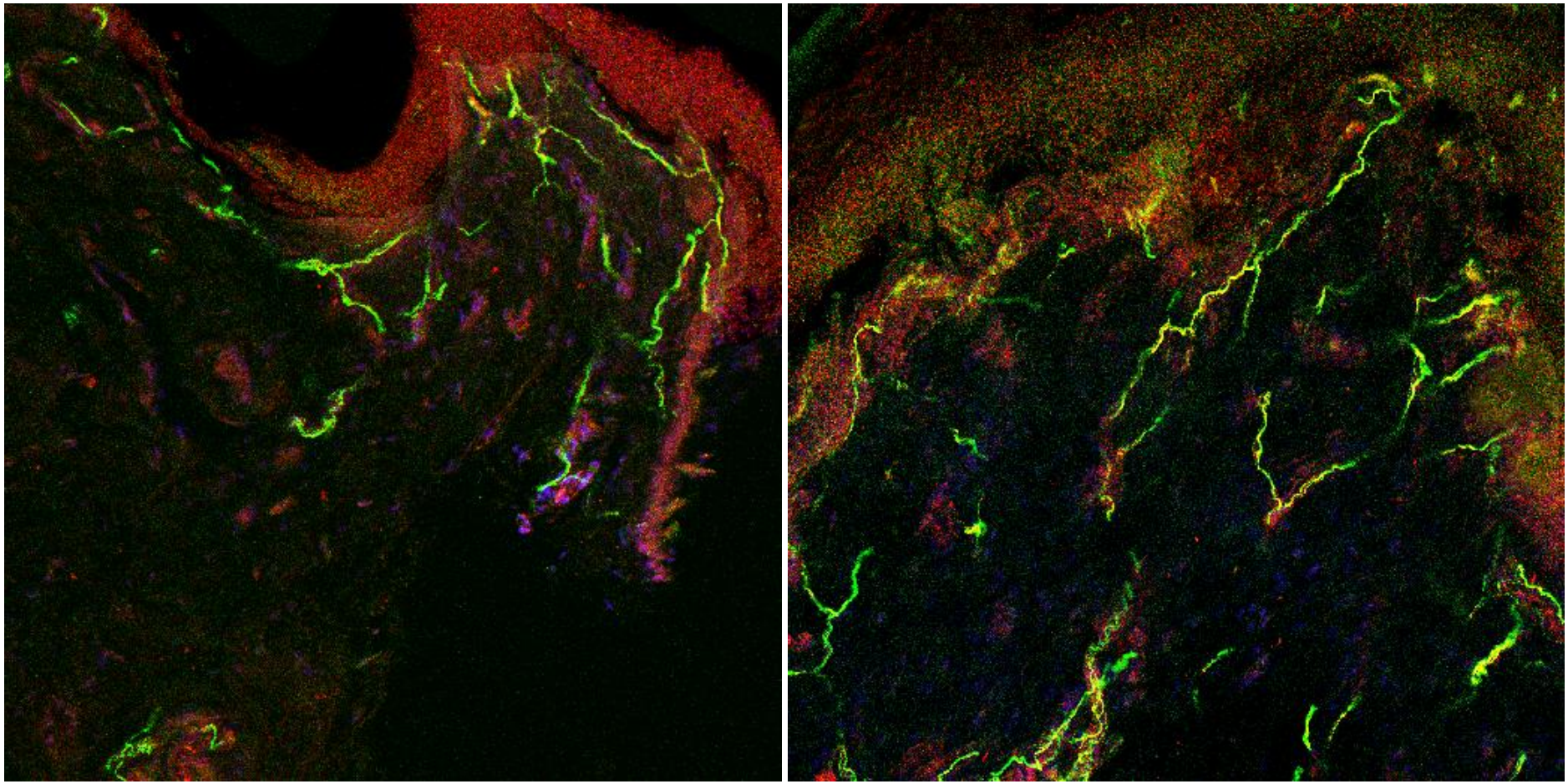
Confocal microscopy shows that MOR-ir is contained in control and inflamed rat paw nerve fibers.



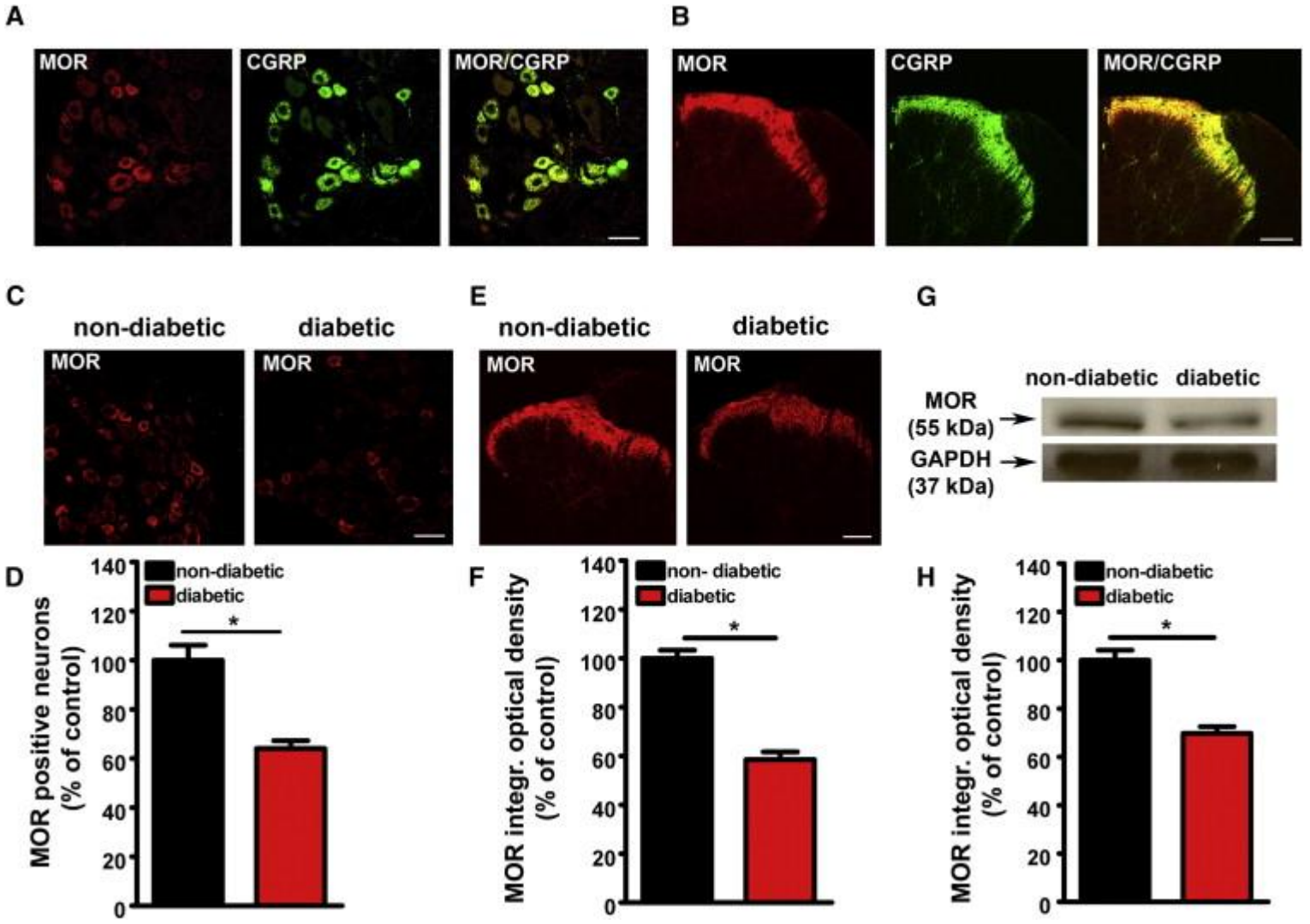
4 days after complete freund adjuvant

Control

Inflamed



4 days after complete freund adjuvant

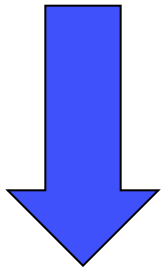

A
MOR
CGRP
MOR/CGRP
B
MOR
CGRP
MOR/CGRP
C
non-diabetic
diabetic
MOR
MOR
E
non-diabetic
diabetic
MOR
MOR
G
non-diabetic
diabetic
MOR
(55 kDa)
GAPDH
(37 kDa)
D
MOR positive neurons
(% of control)
non-diabetic
diabetic
*
0
20
40
60
80
100
120
140
F
MOR integr. optical density
(% of control)
non- diabetic
diabetic
*
0
20
40
60
80
100
120
140
H
MOR integr. optical density
(% of control)
non-diabetic
diabetic
*
0
20
40
60
80
100
120
140

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*).

LOOKING FOR NEW OPIOID ANALGESIC AGENTS WITH LIMITED ACCESS TO CNS



DECREAS IN THE CNS SIDE EFFECTS OF OPIOIDS

HITTING THE PAIN AT ITS SOURCE

0022-3565/05/3122-609–618$20.00
THE JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS

JPET 312:609–618, 2005

Vol. 312, No. 2
75176/1186286
Printed in U.S.A.

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

Department of Pharmacology and Pharmacotherapy, Medical Faculty, Semmelweis University, Budapest, Hungary (S.F., P.R., T.F., J.T., M.A.); Hungarian Academy of Sciences-SE Group of Neuropsychopharmacology, Budapest, Hungary (S.F.); Department of Molecular Neuropharmacology, Institute of Pharmacology, Polish Academy of Sciences, Krakow, Poland (I.O., W.M., R.P., B.P.); and Department of Pharmaceutical Chemistry, Institute of Pharmacy and Center for Molecular Biosciences Innsbruck, University of Innsbruck, Innsbruck, Austria (M.S., J.S., H.S.)

Received July 28, 2004; accepted September 21, 2004

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

ELSEVIER

Brain Research Bulletin 74 (2007) 369–375

BRAIN RESEARCH BULLETIN

www.elsevier.com/locate/brainresbull

Research report

DAMGO and 6β-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[a], Mariana Spetea[b], Tamas Friedmann[a], Pal Riba[a], Kornel Király[a], Helmut Schmidhammer[b], Susanna Furst[a,c,*]

[a] *Department of Pharmacology and Pharmacotherapy, Semmelweis University, Budapest, Hungary*
[b] *Department of Pharmaceutical Chemistry, Institute of Pharmacy and Center for Molecular Biosciences, University of Innsbruck, Innsbruck, Austria*
[c] *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 CNS and
can mediate antinociception at peripheral sites

Brain Research Bulletin 87 (2012) 238–243

Contents lists available at SciVerse ScienceDirect

Brain Research Bulletin

journal homepage: www.elsevier.com/locate/brainresbull

Research report

The central versus peripheral antinociceptive effects of μ-opioid receptor agonists in the new model of rat visceral pain

Mahmoud Al-Khrasani[a,1], Erzsébet Lackó[a,1], Pál Riba[a], Kornél Király[a], Melinda Sobor[a,c], Júlia Timár[a], Shaaban Mousa[b], Michael Schäfer[b], Susanna Fürst[a,*]

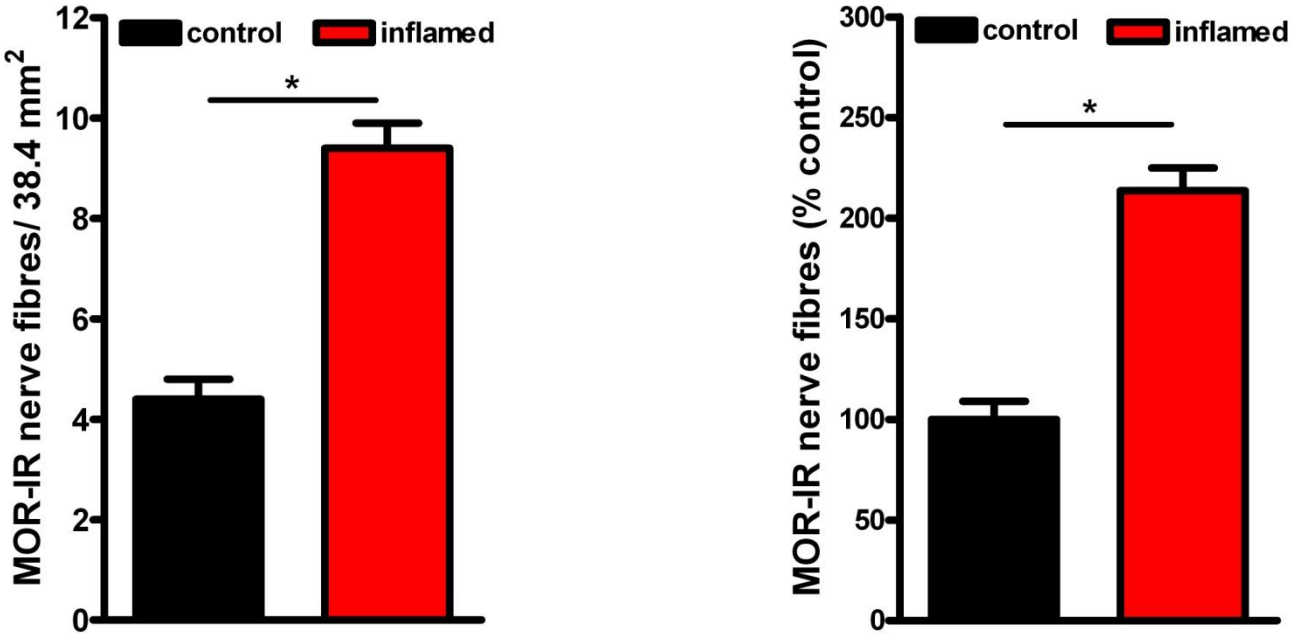
[a] Department of Pharmacology and Pharmacotherapy, Faculty of Medicine, Semmelweis University, Nagyvárad tér 4, P.O. Box 370, H-1445 Budapest, Hungary
[b] Department of Anaesthesiology and Intensive Care Medicine, Charité University Berlin, Campus Virchow Klinikum and Campus Charite Mitte, Berlin, Germany
[c] 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.

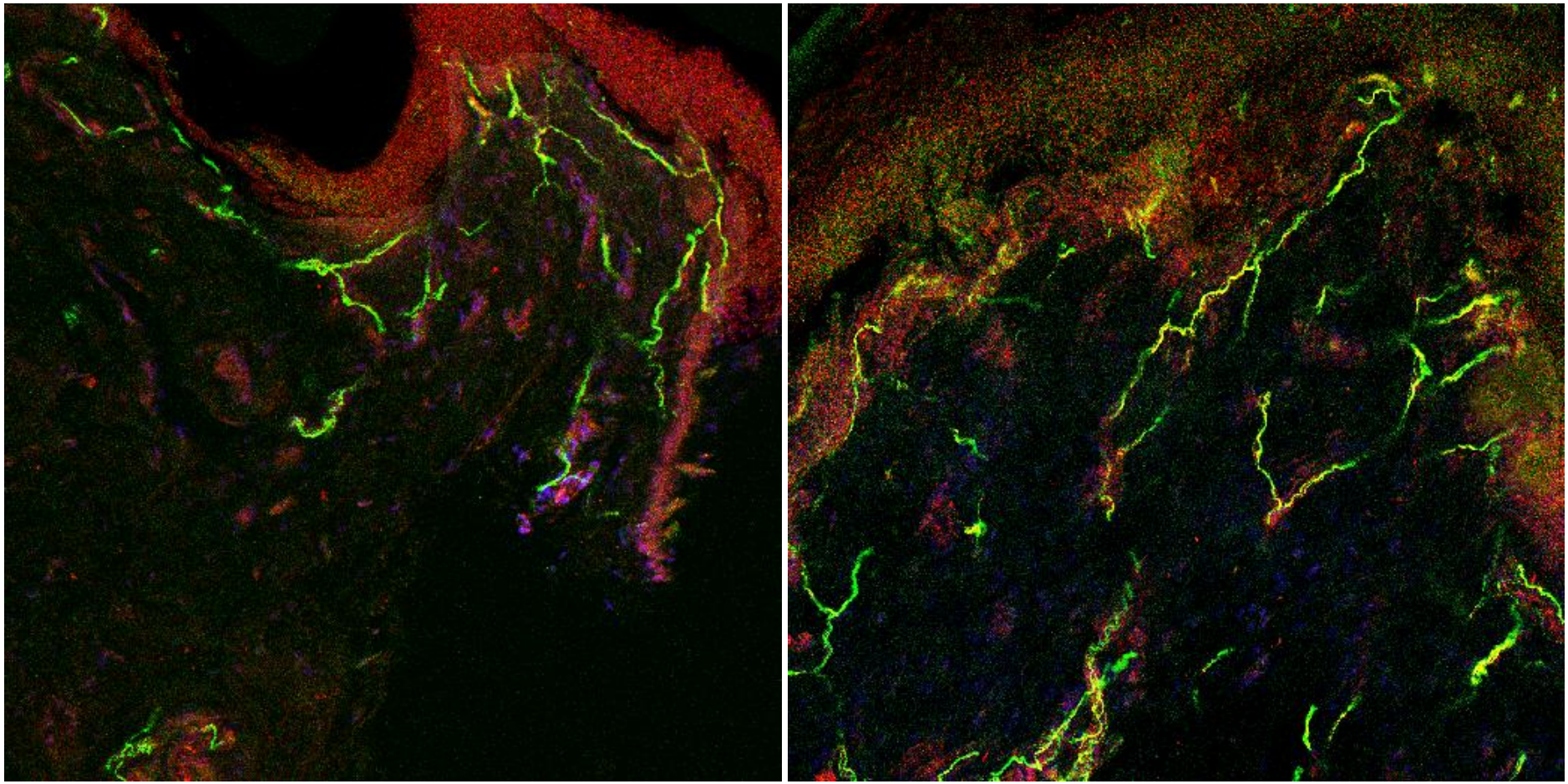
Confocal microscopy shows that MOR-ir is contained in control and inflamed rat paw nerve fibers.



4 days after complete freund adjuvant

Control

Inflamed



4 days after complete freund adjuvant

European Journal of Pharmacology 713 (2013) 54–57

Contents lists available at SciVerse ScienceDirect

European Journal of Pharmacology

journal homepage: www.elsevier.com/locate/ejphar

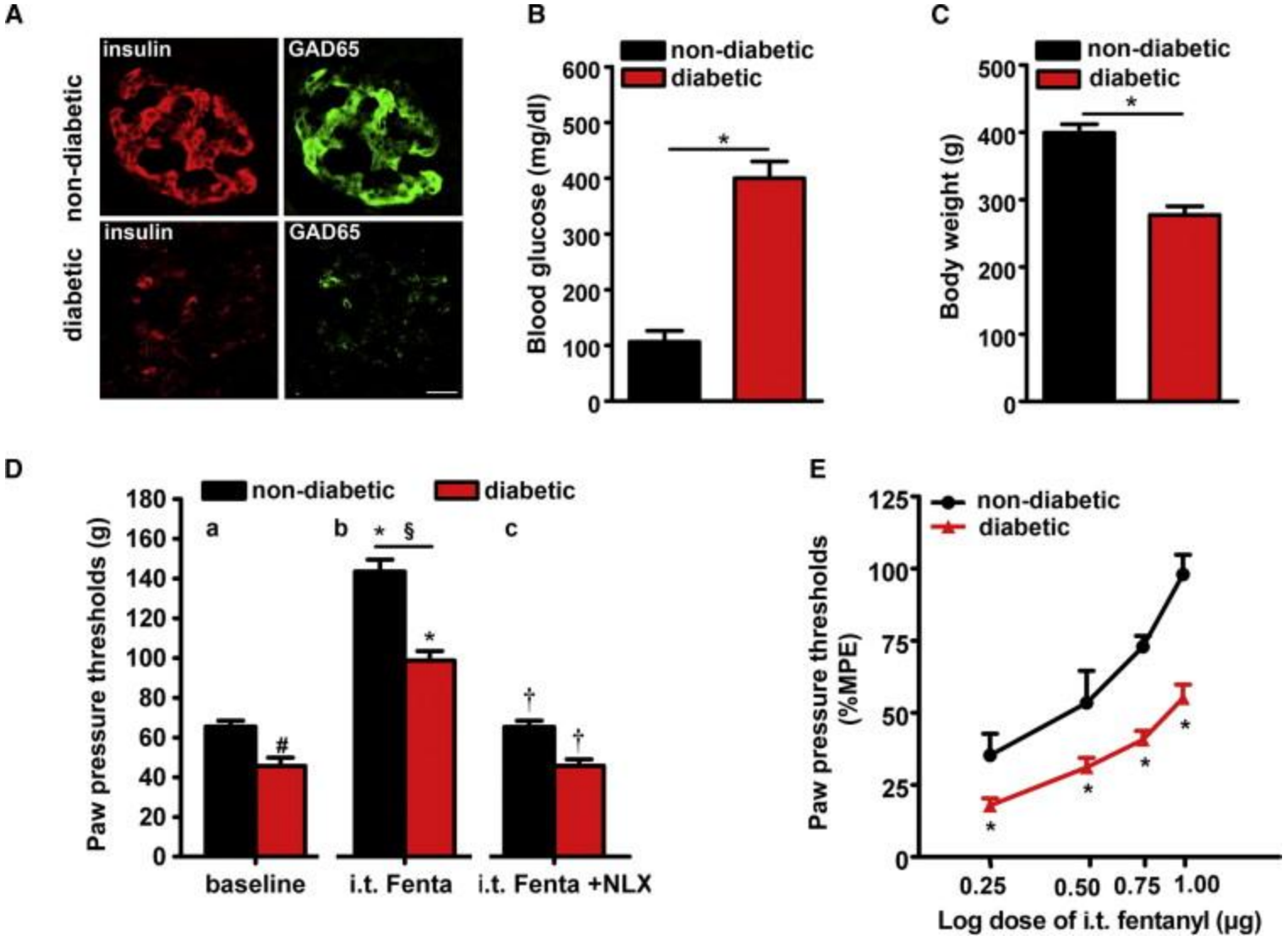
Neuropharmacology and analgesia

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

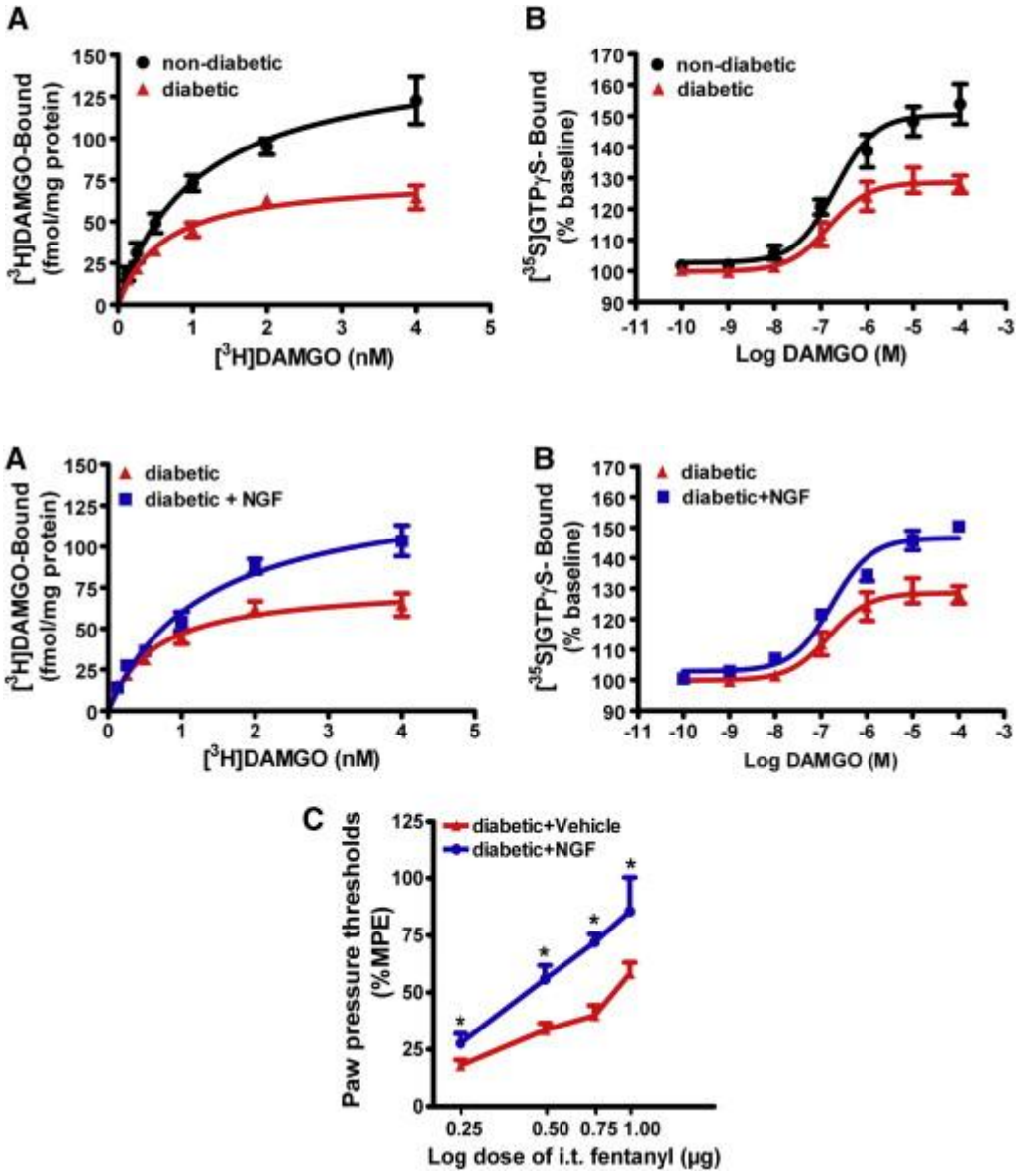
Baled. I. Khalefa [b], Shaaban A. Mousa [b], Mohammed Shaqura [b], Erzsébet Lackó [a], Sándor Hosztafi [c], Pál Riba [a], Michael Schäfer [b], Péter Ferdinandy [a], Susanna Fürst [a], Mahmoud Al-Khrasani [a,*]

[a] *Department of Pharmacology and Pharmacotherapy, Faculty of Medicine, Semmelweis University, Nagyvárad tér 4, P.O. Box 370, H-1445 Budapest, Hungary*
[b] *Department of Anesthesiology and Intensive Care Medicine, Charité University Berlin, Campus Virchow Klinikum and Campus Charite Mitte, Augustnburgerplatz 113353 Berlin, Germany*
[c] *Department of Pharmaceutical Chemistry, Semmelweis University, Hőgyes Endre u., 9. H-1092 Budapest, Hungary*

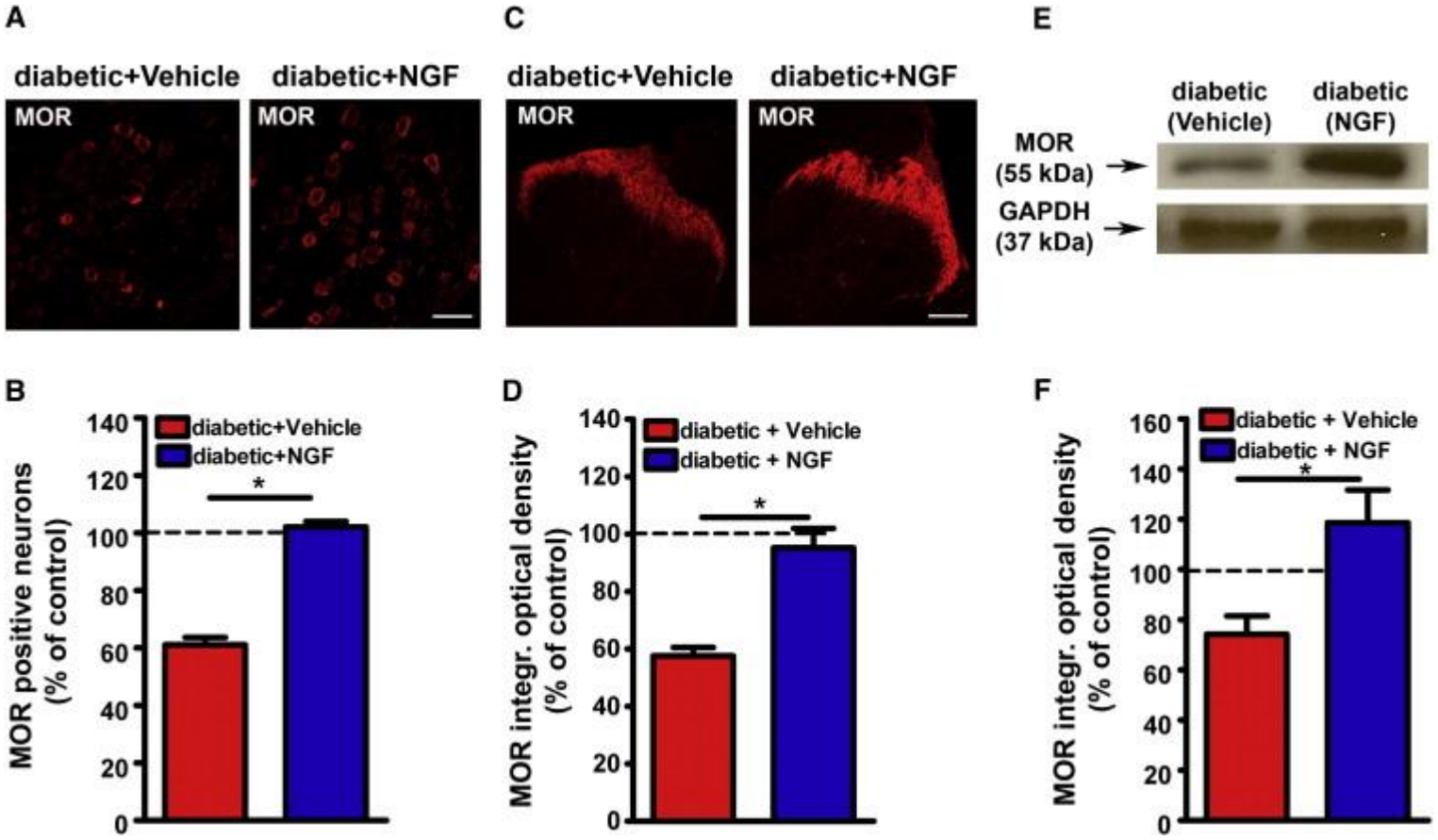
Conclusion: The observed superiority of local antinociceptive effects of 14-*O*-MeM6SU in comparison to non-peptide and peptide opioid agonists might be due to both pharmacodynamic (the efficacy, the receptor reserve and the selectivity) and pharmacokinetic parameters.



The consequences of STZ-treatment in rats



The consequences of STZ-treatment in rats


A
diabetic+Vehicle
diabetic+NGF
MOR
MOR
C
diabetic+Vehicle
diabetic+NGF
MOR
MOR
E
diabetic (Vehicle)
diabetic (NGF)
MOR (55 kDa)
GAPDH (37 kDa)
B
MOR positive neurons (% of control)
diabetic+Vehicle
diabetic+NGF
*
0
20
40
60
80
100
120
140
D
MOR integr. optical density (% of control)
diabetic + Vehicle
diabetic + NGF
*
0
20
40
60
80
100
120
140
F
MOR integr. optical density (% of control)
diabetic + Vehicle
diabetic + NGF
*
0
20
40
60
80
100
120
140
160

American Pain Society
RESEARCH
EDUCATION
TREATMENT
ADVOCACY
PUBLISHED BY ELSEVIER

The Journal of Pain, Vol 14, No 7 (July), 2013: pp 720-730
Available online at www.jpain.org and www.sciencedirect.com

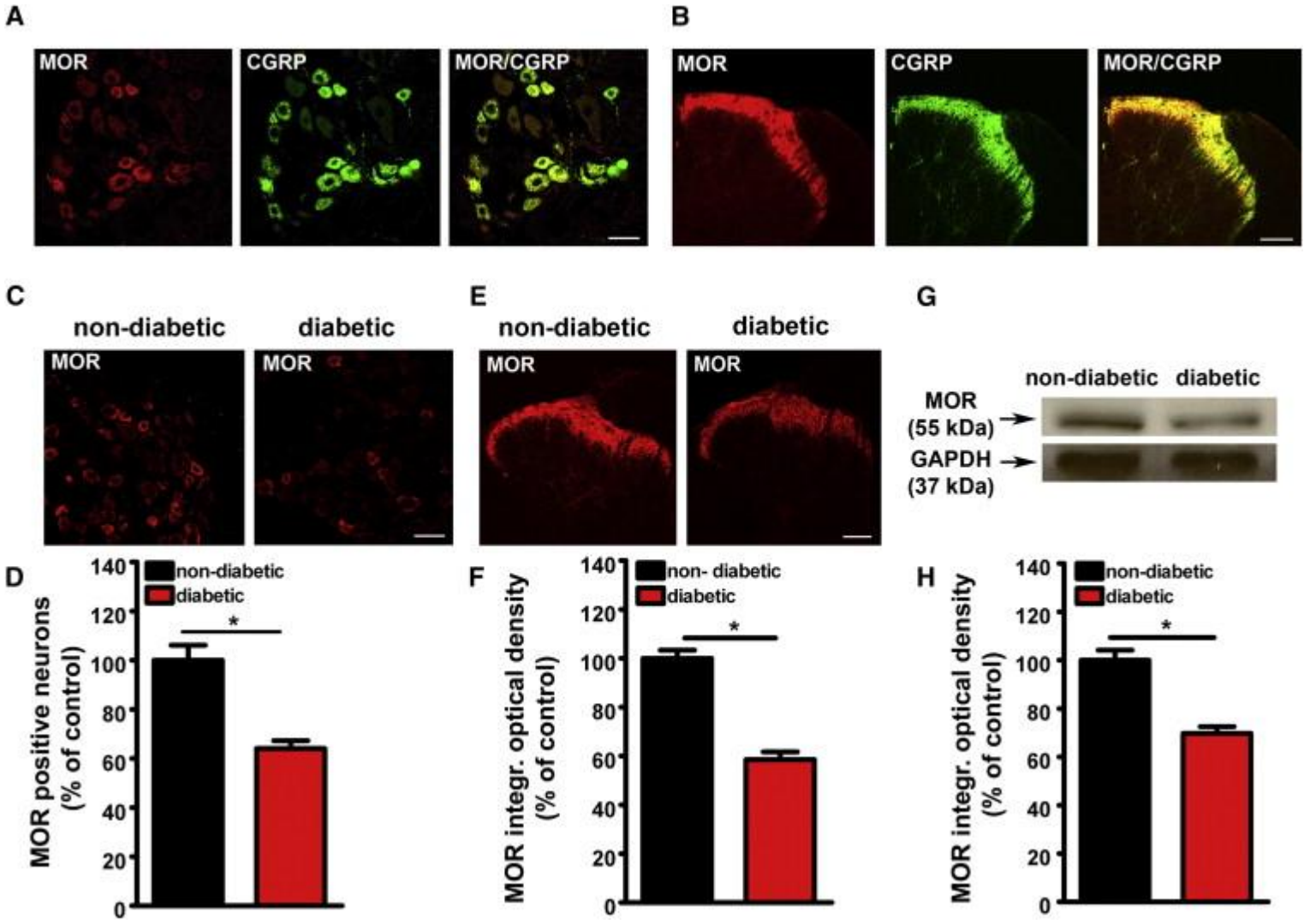
Reduced Number, G Protein Coupling, and Antinociceptive Efficacy of Spinal Mu-Opioid Receptors in Diabetic Rats Are Reversed by Nerve Growth Factor

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

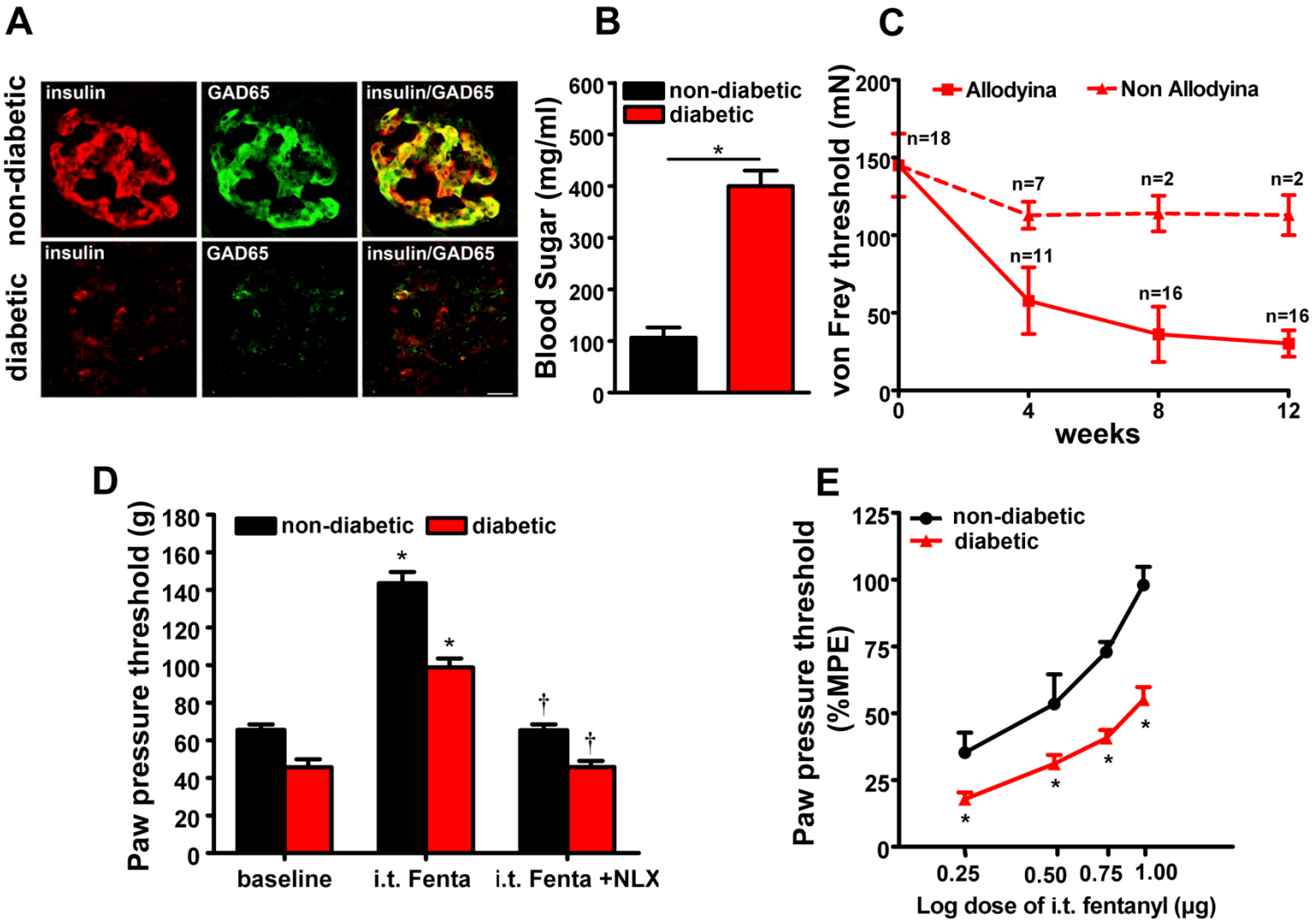
**Department of Anaesthesiology and Intensive Care Medicine, Charité University Berlin, Campus Virchow Klinikum and Campus Charite Mitte, Berlin, Germany.*
†Department of Anatomy, Ludwig-Maximilian-University Munich, Germany.
‡Department of Pharmacology and Pharmacotherapy, Semmelweis University, Budapest, Hungary.

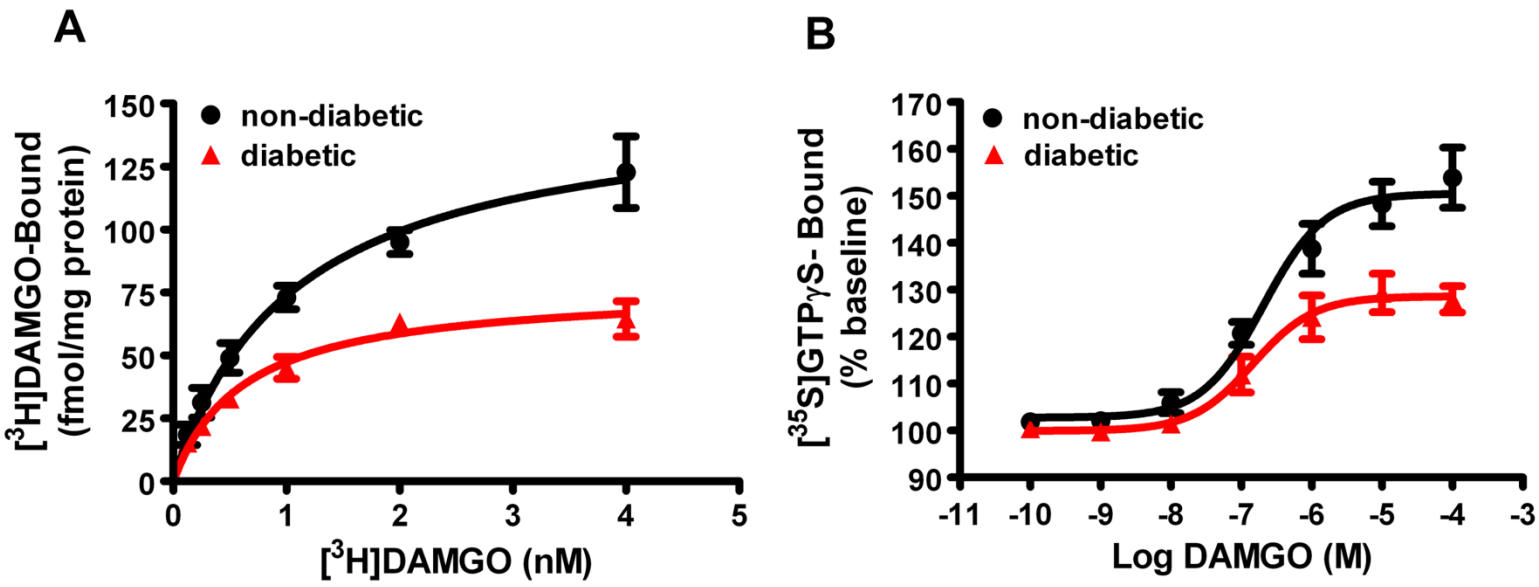
For the first time we show a loss in MOR-IR neurons, membrane-spanning receptors, and functional G protein coupling during advanced STZ-induced diabetes as a contributing factor for the impaired antinociception of i.t.-delivered MOR opioid agonists.

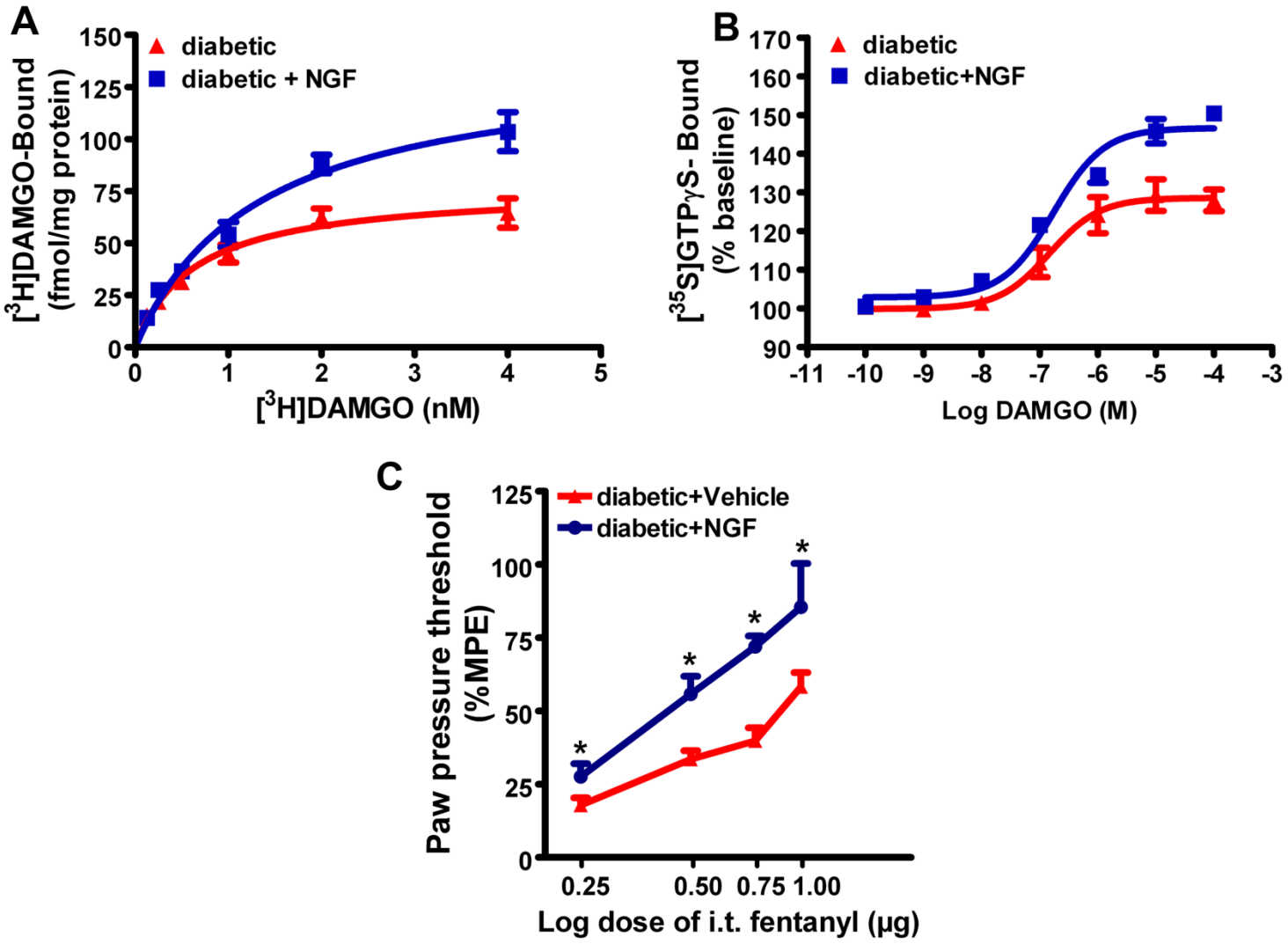
Pretreatment with i.t. NGF reversed these alterations and rescued opioid responsiveness.



The μ-opioid receptors (MOR) density in diabetic and non-diabetic rats


A
non-diabetic
diabetic
insulin
GAD65
insulin/GAD65
insulin
GAD65
insulin/GAD65
B
Blood Sugar (mg/ml)
600
500
400
300
200
100
0
non-diabetic
diabetic
*
C
von Frey threshold (mN)
200
150
100
50
0
Allodyina
Non Allodyina
n=18
n=7
n=2
n=2
n=11
n=16
n=16
0
4
8
12
weeks
D
Paw pressure threshold (g)
180
160
140
120
100
80
60
40
20
0
non-diabetic
diabetic
*
*
†
†
baseline
i.t. Fenta
i.t. Fenta +NLX
E
Paw pressure threshold (%MPE)
125
100
75
50
25
0
non-diabetic
diabetic
*
*
*
*
0.25
0.50
0.75
1.00
Log dose of i.t. fentanyl (µg)


A
non-diabetic
diabetic
[3H]DAMGO-Bound
(fmol/mg protein)
150
125
100
75
50
25
0
0
1
2
3
4
5
[3H]DAMGO (nM)
B
non-diabetic
diabetic
[35S]GTPγS- Bound
(% baseline)
170
160
150
140
130
120
110
100
90
-11
-10
-9
-8
-7
-6
-5
-4
-3
Log DAMGO (M)


A
diabetic
diabetic + NGF
[3H]DAMGO-Bound (fmol/mg protein)
150
125
100
75
50
25
0
0
1
2
3
4
5
[3H]DAMGO (nM)
B
diabetic
diabetic+NGF
[35S]GTPγS- Bound (% baseline)
170
160
150
140
130
120
110
100
90
-11
-10
-9
-8
-7
-6
-5
-4
-3
Log DAMGO (M)
C
diabetic+Vehicle
diabetic+NGF
Paw pressure threshold (%MPE)
125
100
75
50
25
0
*
*
*
*
0.25
0.50
0.75
1.00
Log dose of i.t. fentanyl (µg)

Neuropharmacology 85 (2014) 142–150

Contents lists available at ScienceDirect

Neuropharmacology

journal homepage: www.elsevier.com/locate/neuropharm

New insights into mechanisms of opioid inhibitory effects on capsaicin-induced TRPV1 activity during painful diabetic neuropathy

Mohammed Shaqura [a], Baled.I. Khalefa [a], Mehdi Shakibaei [b], Christian Zöllner [c], Mahmoud Al-Khrasani [d], Susanna Fürst [d], Michael Schäfer [a], Shaaban A. Mousa [a, *]

[a] *Department of Anaesthesiology and Intensive Care Medicine, Charité University Berlin, Campus Virchow Klinikum and Campus Charite Mitte, Augustenburgerplatz 1, 13353 Berlin, Germany*
[b] *Department of Anatomy, Ludwig-Maximilian-University Munich, Germany*
[c] *Department of Anaesthesiology, Universitätsklinikum Hamburg Eppendorf, Hamburg, Germany*
[d] *Department of Pharmacology and Pharmacotherapy, Semmelweis University, Budapest, Hungary*

1521-0103/359/1/171–181$25.00
THE JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS

http://dx.doi.org/10.1124/jpet.116.233551
J Pharmacol Exp Ther 359:171–181, October 2016

nd Experimental Therapeutics

New Morphine Analogs Produce Peripheral Antinociception within a Certain Dose Range of Their Systemic Administration

Erzsébet Lackó, Pál Riba, Zoltán Giricz, András Váradi, Laura Cornic, Mihály Balogh, Kornél Király, Kata Csekő, Shaaban A. Mousa, Sándor Hosztafi, Michael Schäfer, Zoltán Sándor Zádori, Zsuzsanna Helyes, Péter Ferdinandy, Susanna Fürst, and Mahmoud Al-Khrasani

Departments of Pharmacology and Pharmacotherapy (E.L., P.R., Z.G., L.C., M.B., K.K., Z.S.Z., P.F., S.F., M.A.) and Pharmaceutical Chemistry (A.V., S.H.), Faculty of Medicine, Semmelweis University, Budapest, Hungary; Department of Anaesthesiology and Intensive Care Medicine, Charité University Berlin, Campus Virchow Klinikum and Campus Charité Mitte, Berlin, Germany (S.A.M., M.S.); Department of Pharmacology and Pharmacotherapy, Medical School, Szentágothai Research Centre (K.C., Z.H.), and MTA-PTE NAP B Chronic Pain Research Group, Faculty of Medicine (Z.H.), University of Pécs, Pécs, Hungary

Received March 16, 2016; accepted July 18, 2016

Titration of systemic doses of opioid compounds with limited access to the brain might offer peripheral analgesia of clinical importance. These data indicate that the development of opioid drugs like M6SU and its analogues, which hit the pain in the periphery with a wide safety index, may represent a new opioid generation for the treatment of inflammatory pain.