M-TYPE K^+ CHANNELS IN NOCICEPTIVE PATHWAYS: PHYSIOLOGICAL ROLES AND THERAPEUTIC POTENTIAL

Nikita Gamper

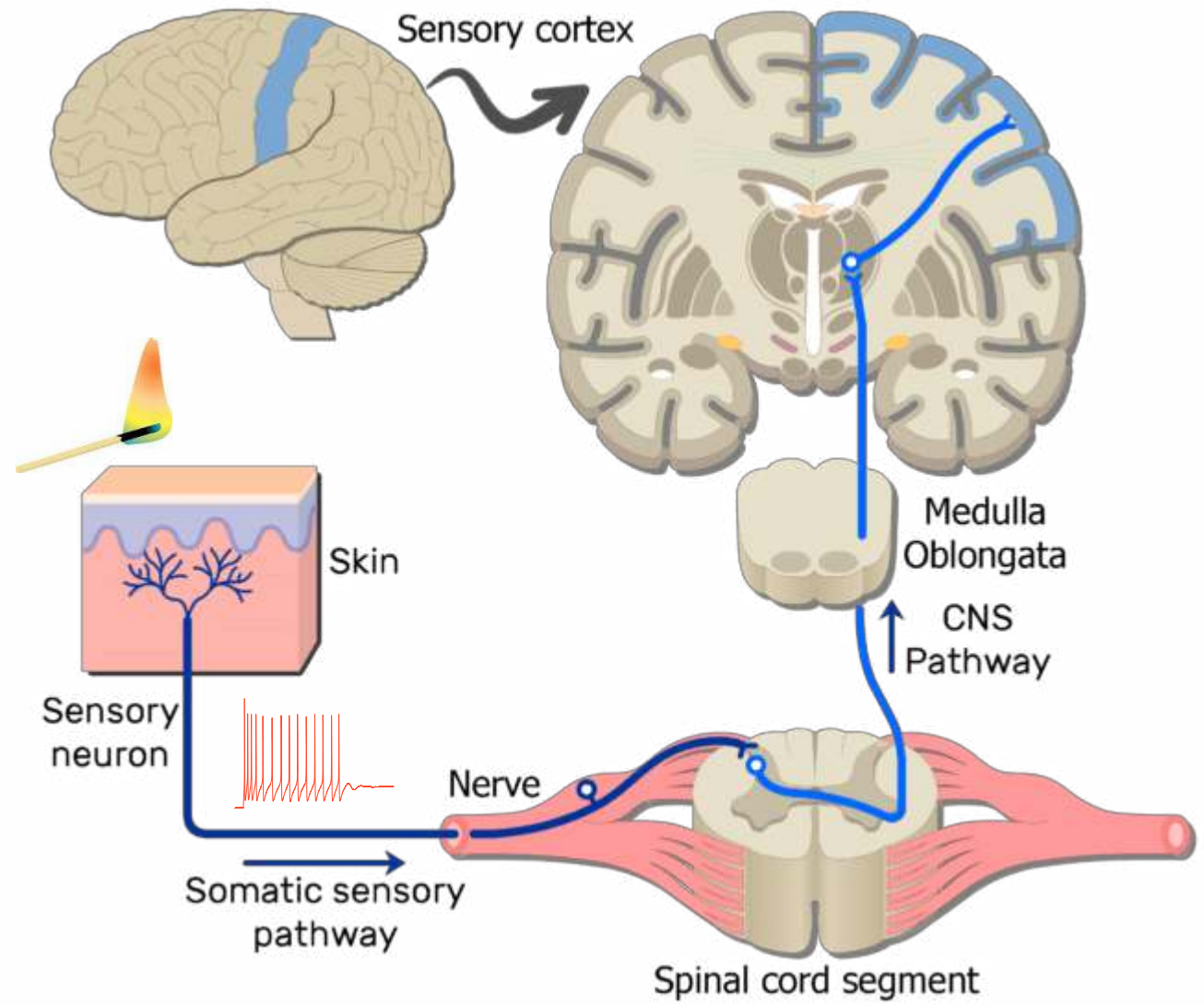
February 5th 2019

Metrion Bioscience

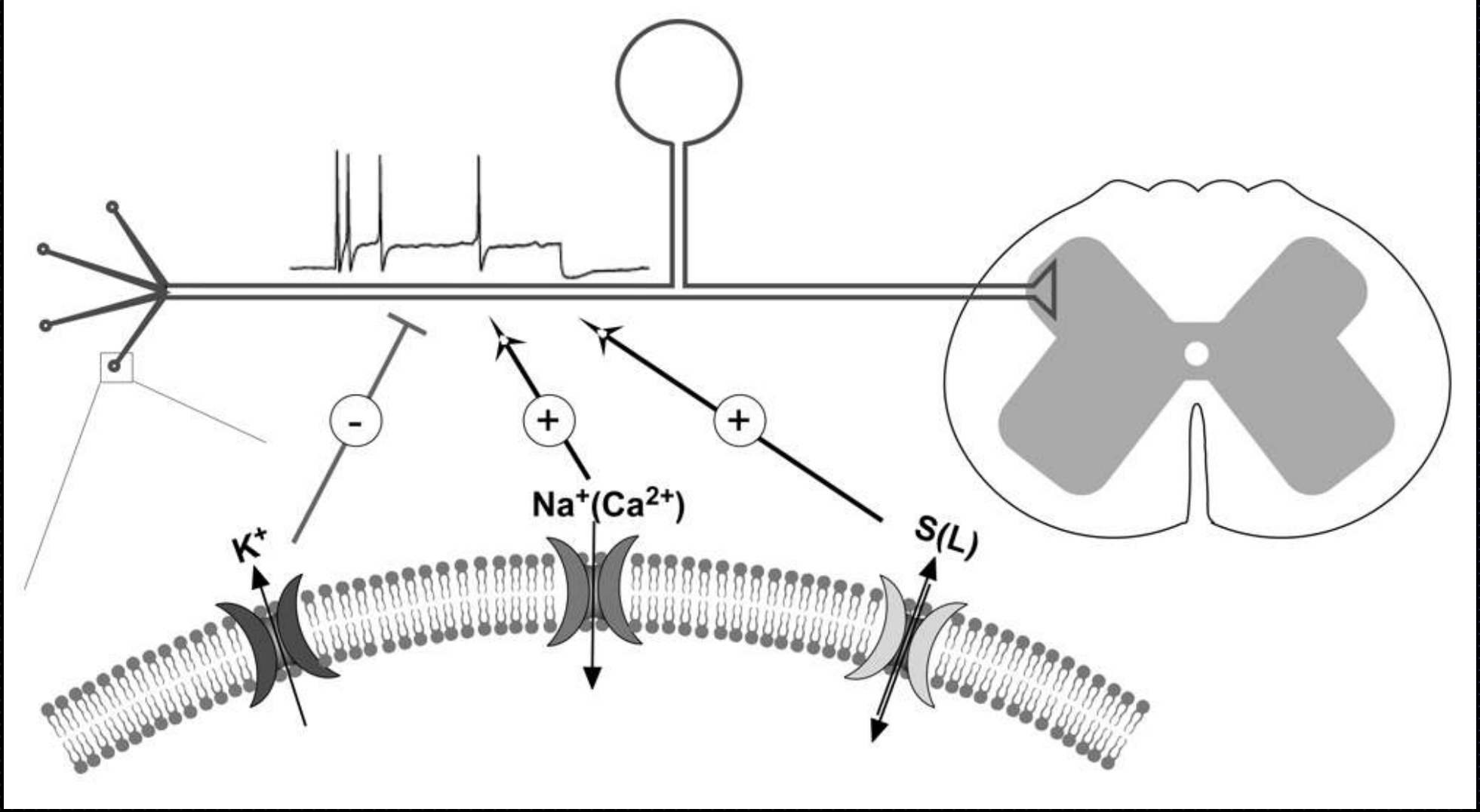
PAIN IN NUMBERS:

- In European countries, national annual economic costs of chronic pain amounts to **3–10% of gross domestic products**
- In US total incremental cost of health care due to pain ranged from $261 to $300 billion p. a…. **nearly 30 percent higher than the combined cost of cancer and diabetes.**
- Analgesics Market is Expected to Reach **$26.4 Billion,** Globally, by 2022

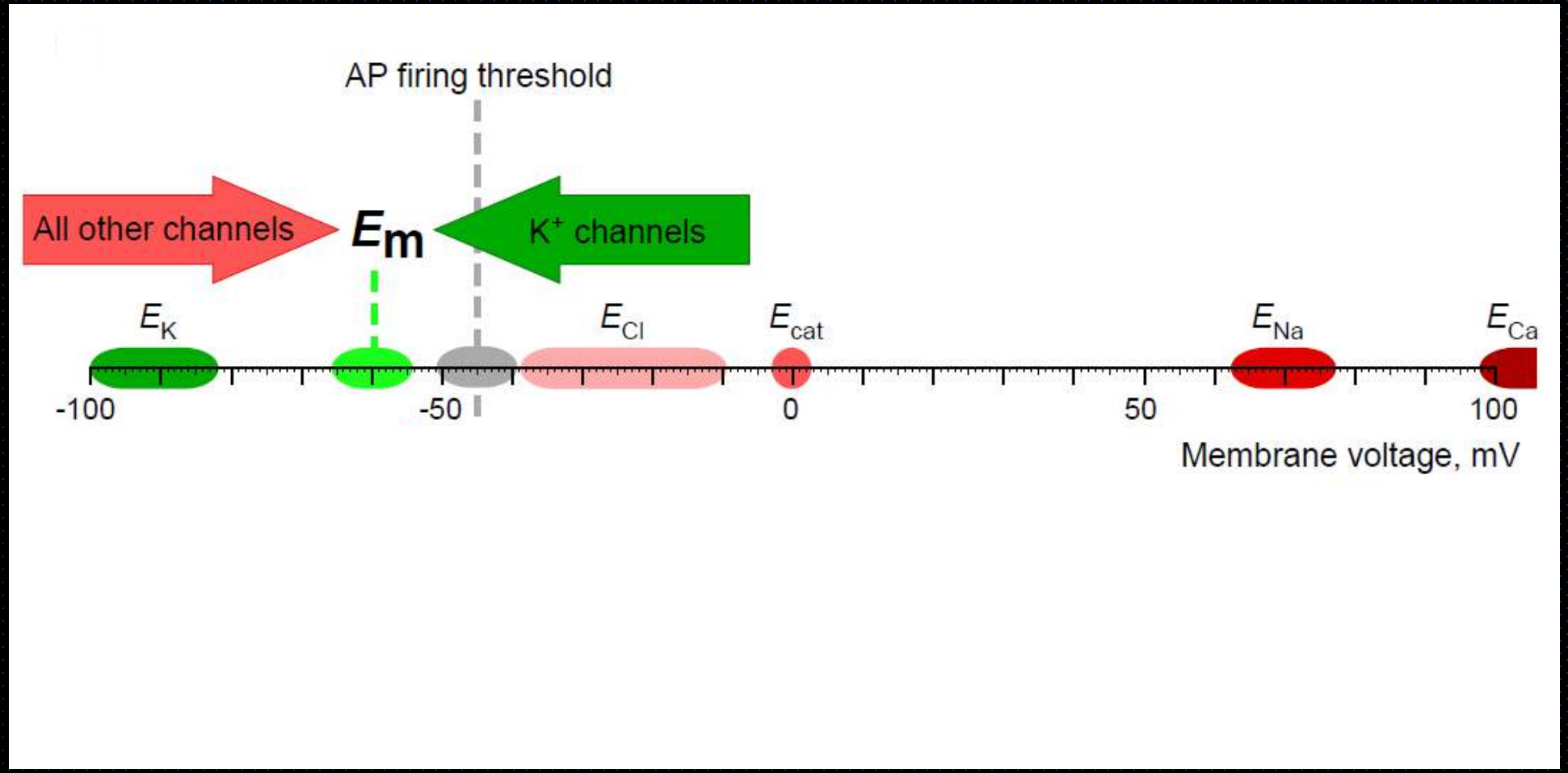
Excitability of sensory neurons is a way to communicate sensory information to the brain



Primary nociceptive signal is formed when an action potential is fired by nociceptive neuron



K^+ channels are the only channels in sensory neurons that drive resting membrane potential towards hyperpolarizing voltages



Du & Gamper (2013) Current Neuropharmacol

Chronic pain is a most common symptom of K^+ channel autoimmunity

AMERICAN ACADEMY OF NEUROLOGY.
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The Official Journal of the American Academy of Neurology

Chronic pain as a manifestation of potassium channel-complex autoimmunity

Christopher J. Klein, MD
Vanda A. Lennon, MD, PhD
Paula A. Aston, MD
Andrew McKeon, MD

ABSTRACT

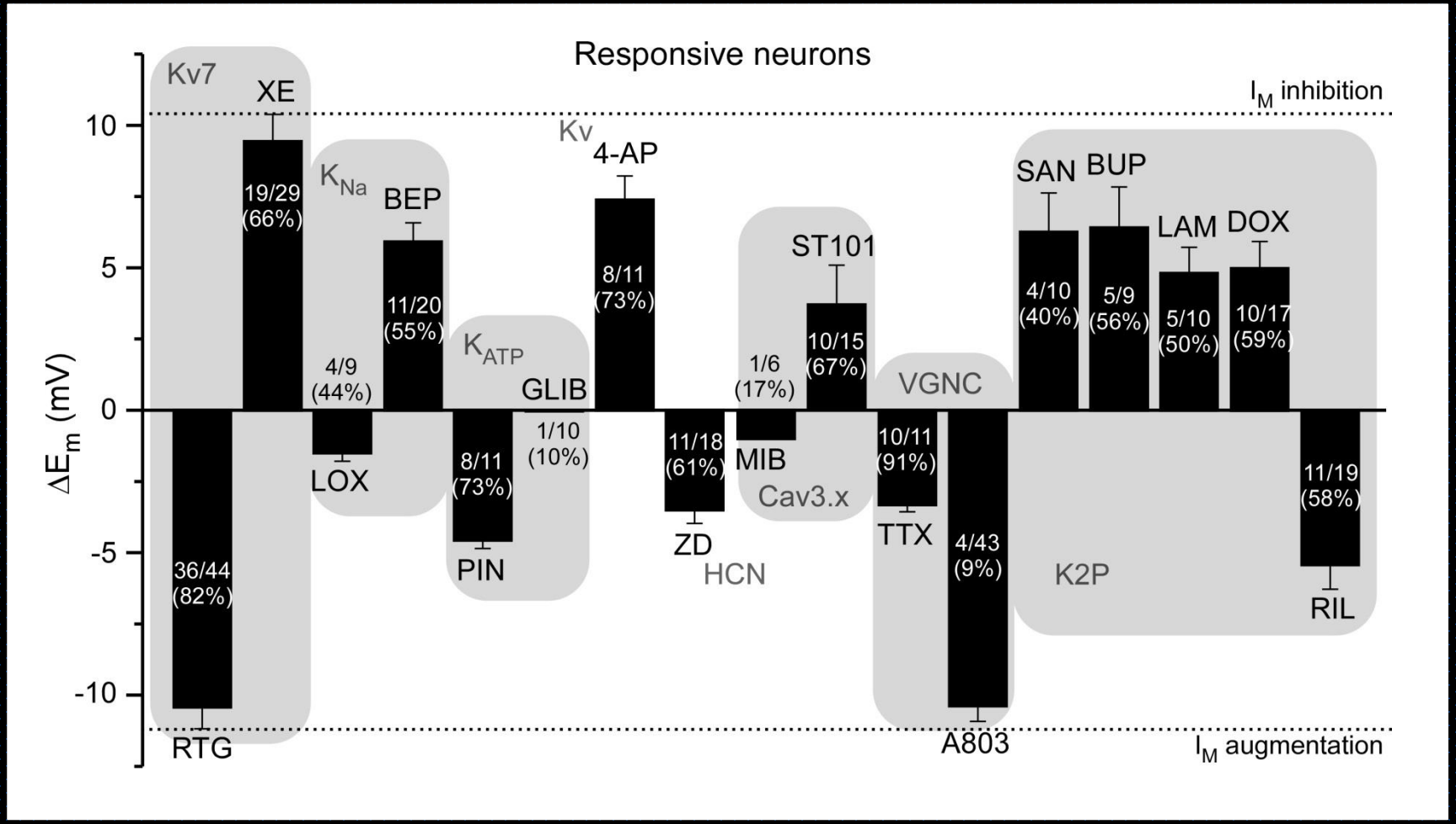
Objective: Autoantibodies targeting voltage-gated potassium channel (VGKC) complexes cause a spectrum of neuronal hyperexcitability disorders. We investigated pain as a manifestation of VGKC-complex autoimmunity.

Methods: We reviewed the prevalence and characteristics of pain in VGKC-complex-immunoglobulin G (IgG)–seropositive patients in 25 months of comprehensive service testing for

Results: VGKC-complex-IgG was identified in 1,992 patients of 54,853 tested (4%). Of 316 evaluated neurologically at Mayo Clinic, 159 (50%) had pain, in isolation (28%) or with accompanying neurologic manifestations (72%), and not attributable to alternative cause. Pain was subacute in onset, chronic in course, neuropathic, nociceptive, regional, or diffuse and sometimes attributed to fibromyalgia (6%) or psychogenic cause (13%). Most patients had normal peripheral nervous system function, measured by neuropathy impairment scores and nerve conduction. Evidence of neuronal hyperexcitability (hyperhidrosis, quantitative heat-pain hyperalgesia, or electromyographic excitability) was 25-fold more common in pain patients. Pain management required multiple medications in 70% (narcotics, 30%); 13 of 16 patients reported pain relief

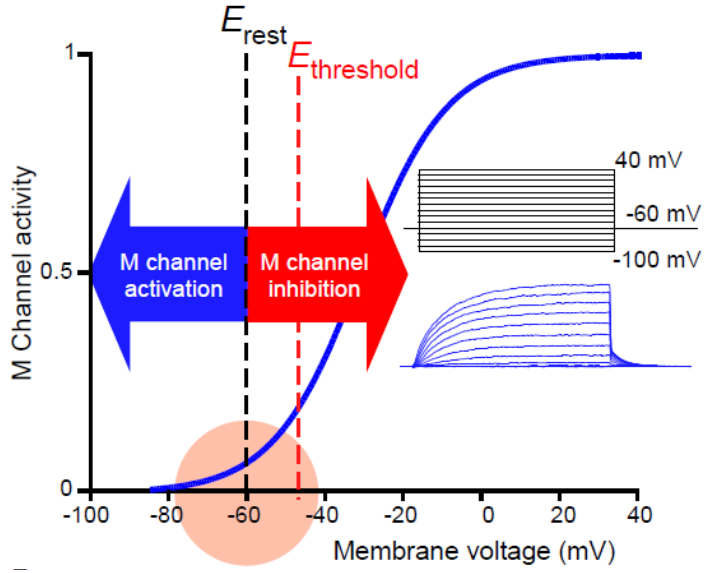
Conclusions: Chronic idiopathic pain is a syndromic manifestation of VGKC-complex autoimmunity. Hyperexcitability of nociceptive pathways is implicated. CASPR2-IgG significantly associates with pain, but in most patients the antigenic VGKC-complex molecule remains to be determined. VGKC-complex autoimmunity represents an important new direction for pain research and therapy. *Neurology*® 2012;79:1136–1144

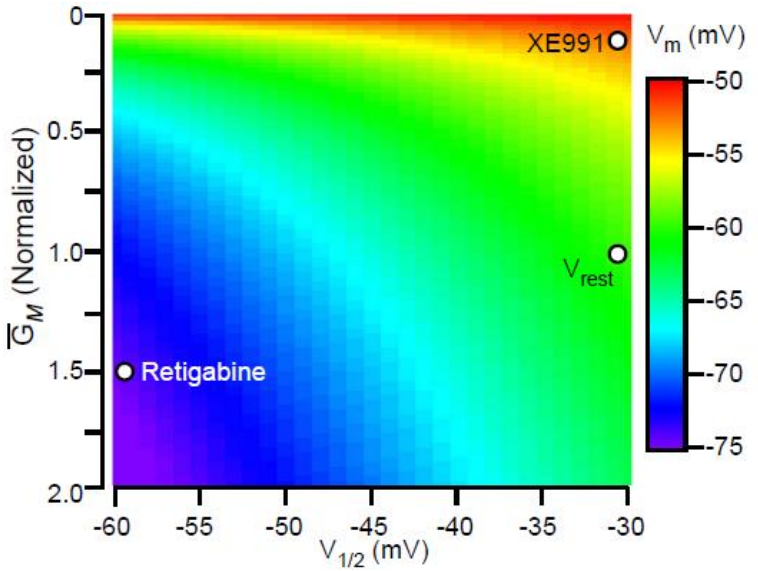
Our screen for the ‘resting’ currents in DRG neurons identified current generated by M-type K^+ channels as a dominant ‘controller’ of resting membrane potential

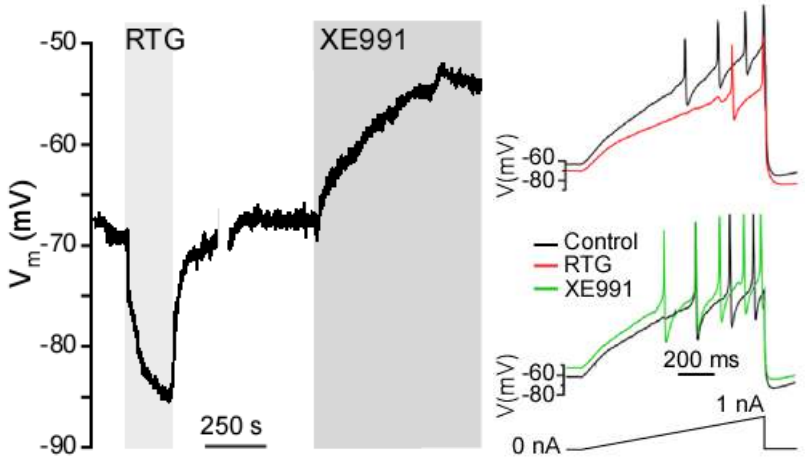


Du et al. (2014) PAIN

M channels: fit to control



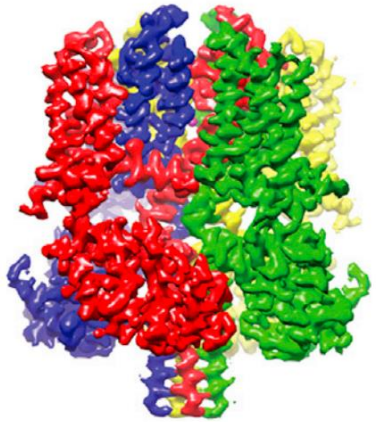




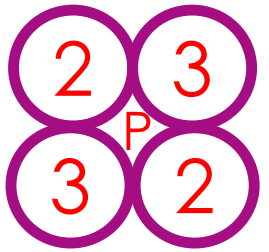
Du et al. (2018) BJP

KCNQ1 at 3.7Å:

Sun & MacKinnon Cell 2017

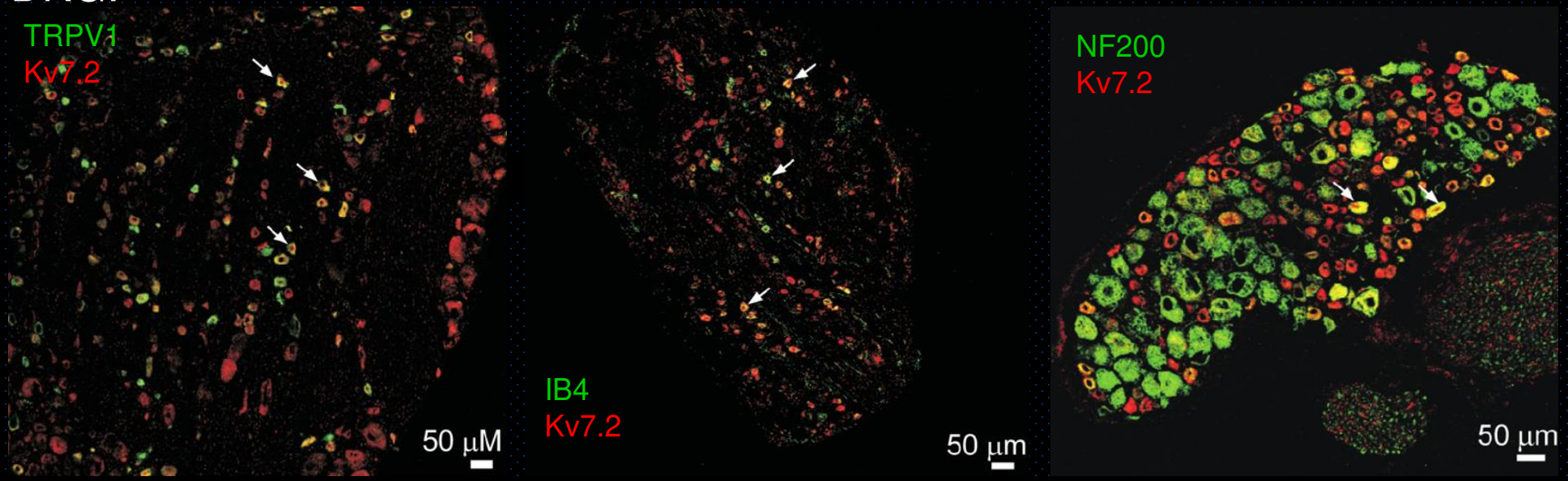


Neuronal M channel

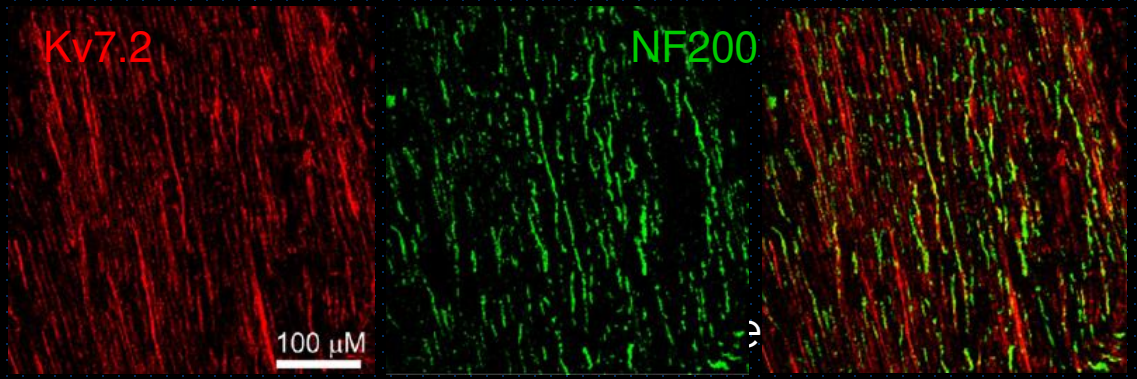


M channel subunit Kv7.2 is abundantly expressed in peripheral sensory fibres

DRG:

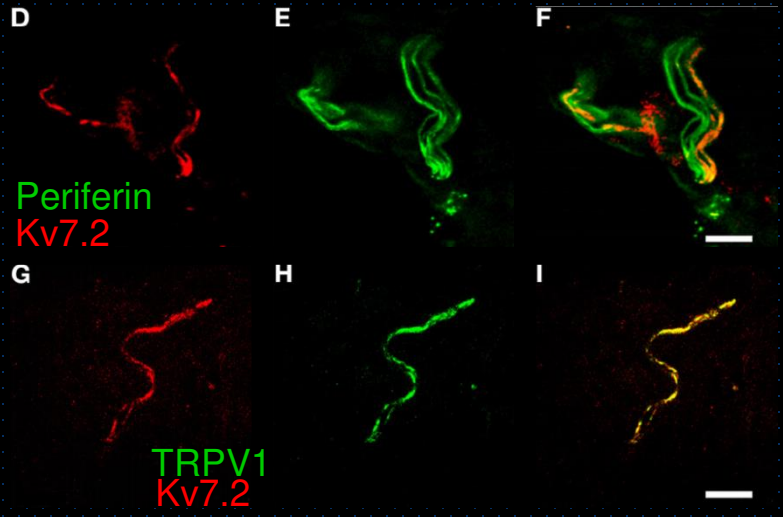


Sciatic nerve:



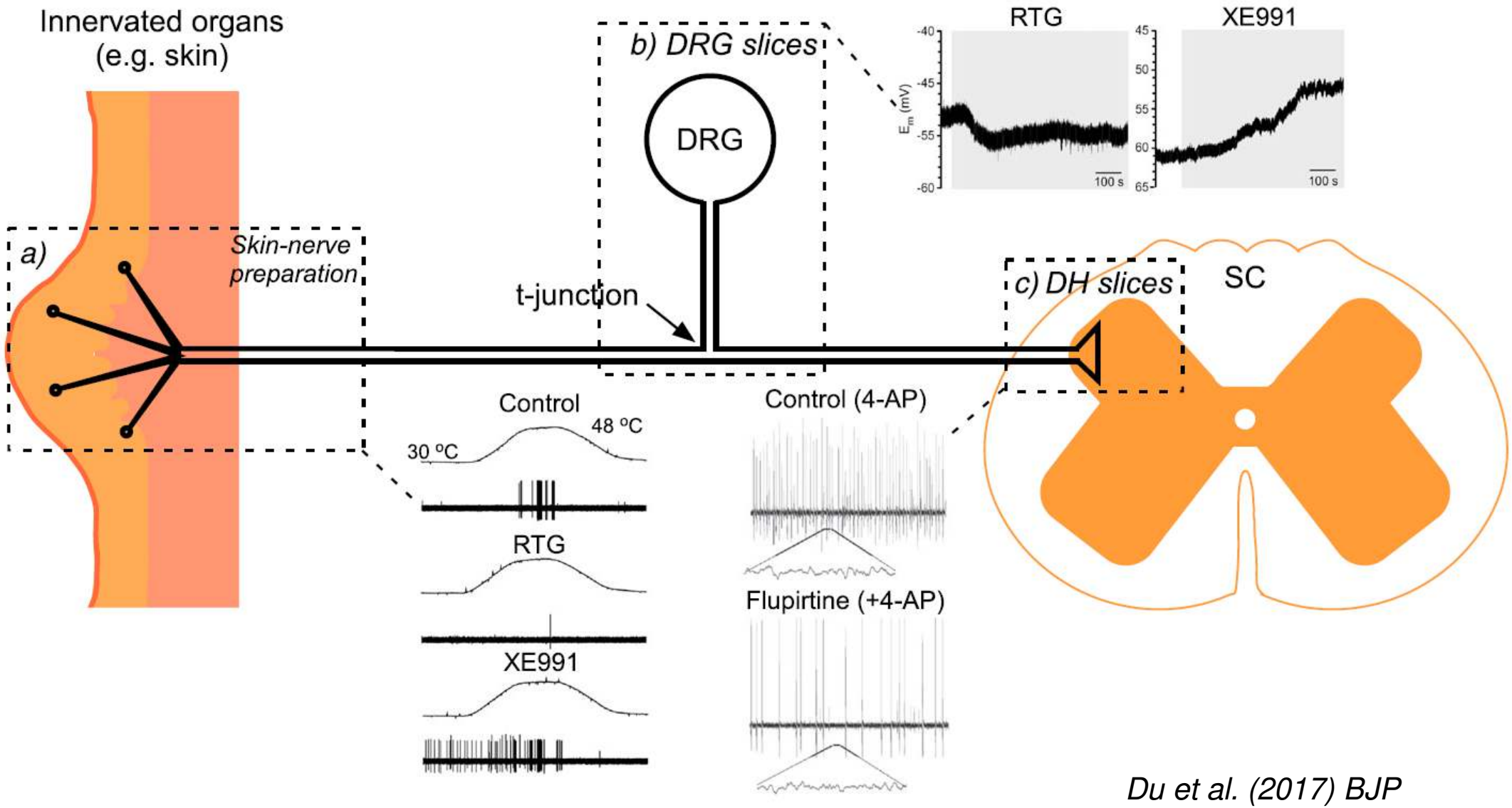
Rose et al. (2011) PAIN

Skin endings:



Passmore et al. (2012) Front Mol Neurosci

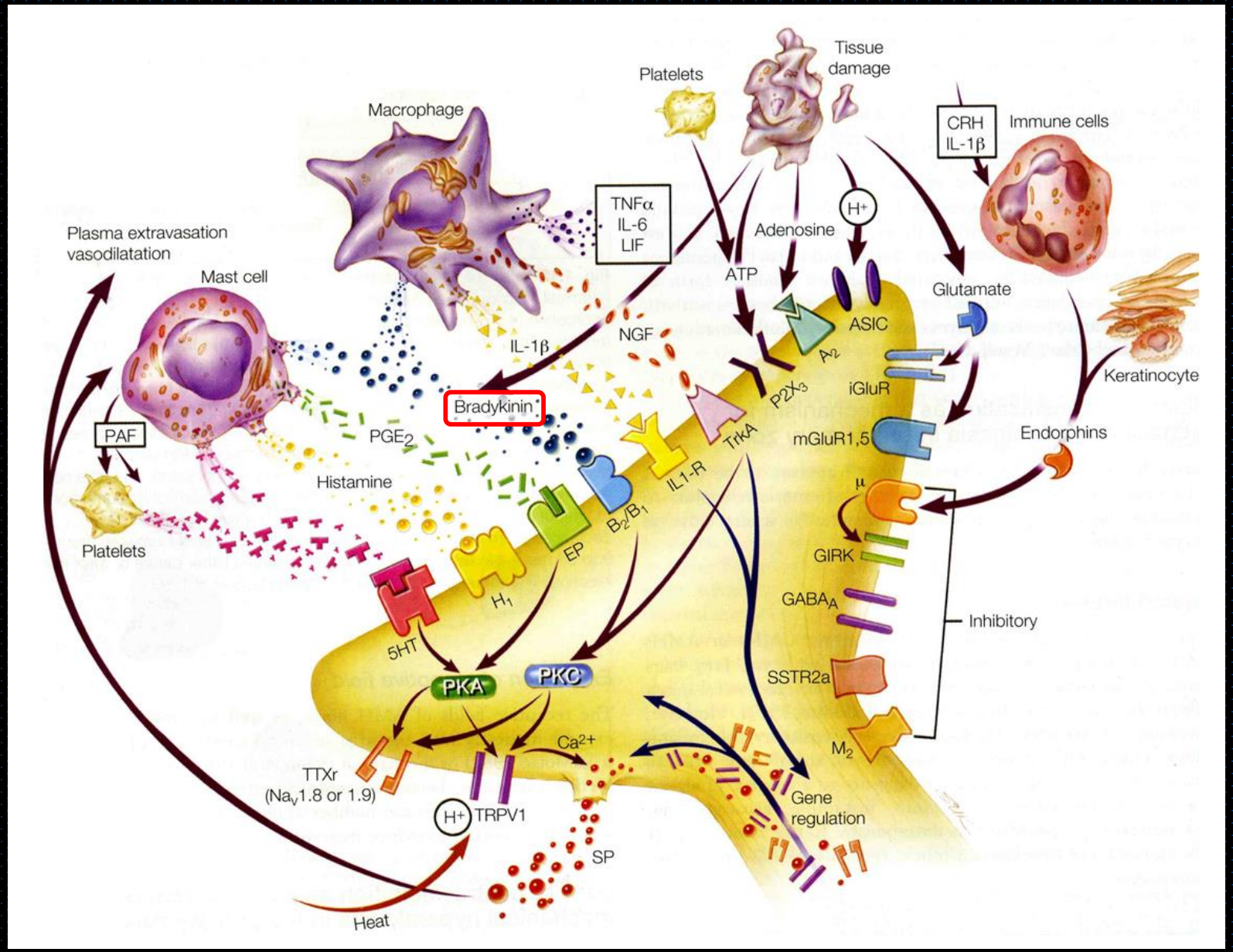
Functional M channels are expressed along the major compartments of a peripheral somatosensory neuron



Du et al. (2017) BJP

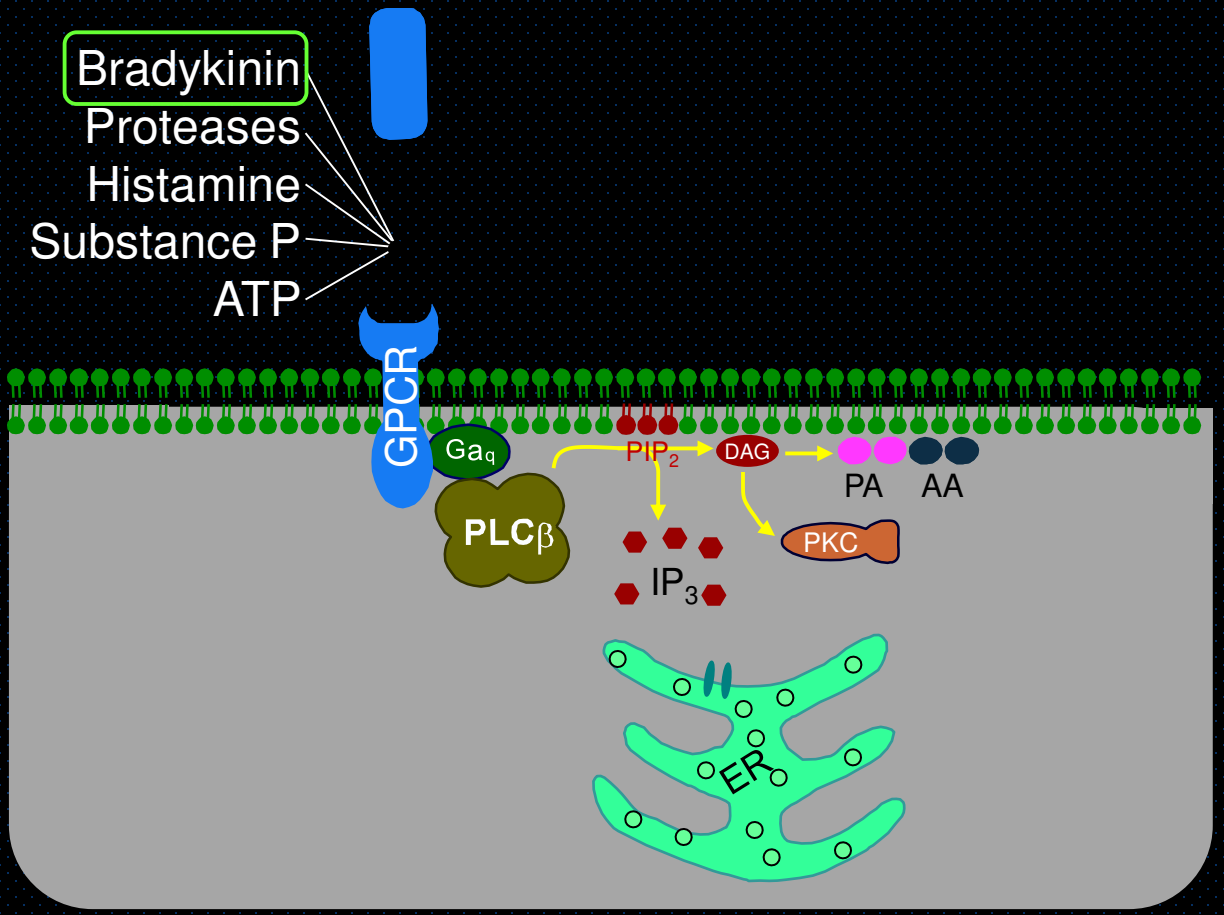
Role of M channels in inflammatory pain

Chemical mediators of inflammatory pain

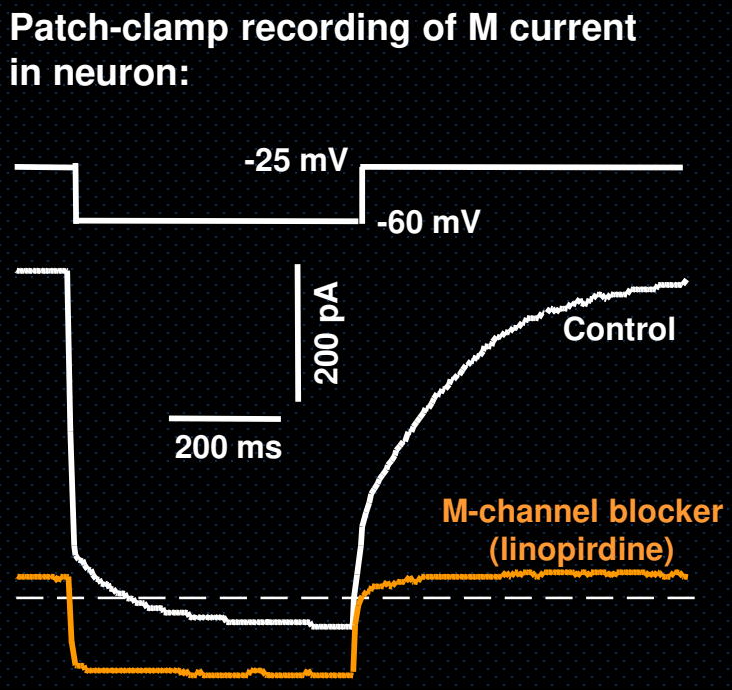


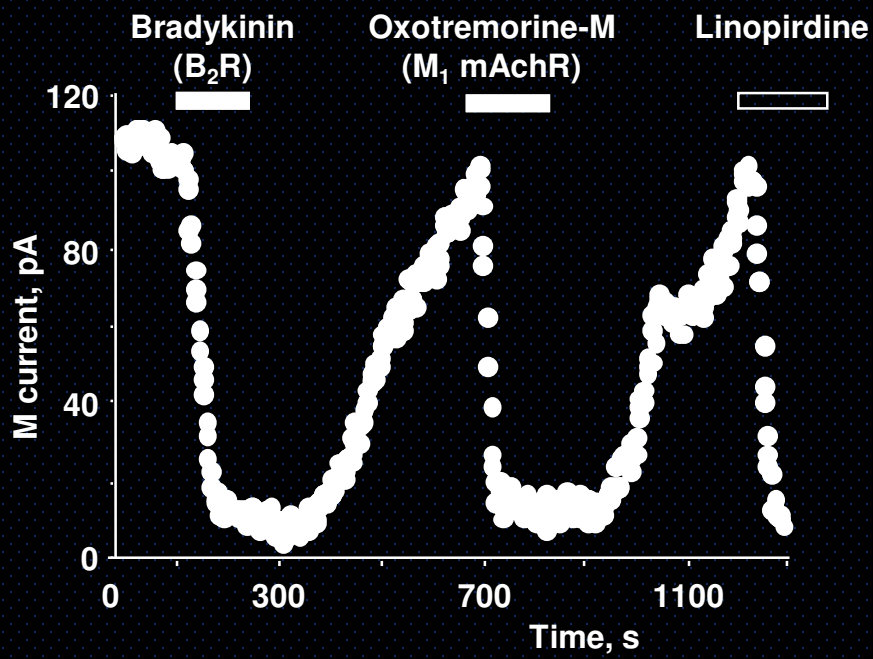
Wall and Melzack's Textbook of Pain

Several inflammatory mediators act trough $G_{q/11}$-coupled receptors expressed in sensory neurons

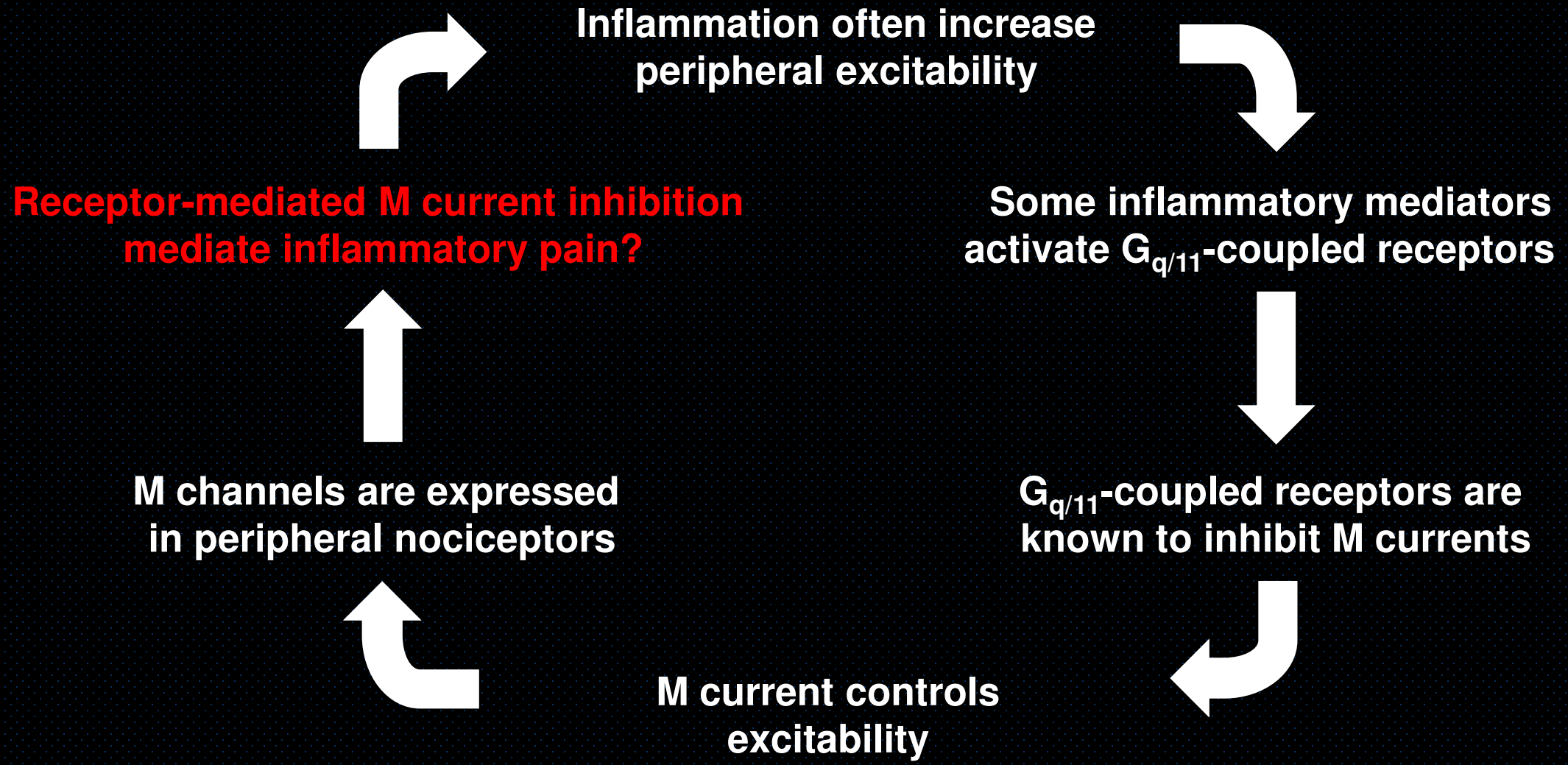


$G_{q/11}$-coupled receptors inhibit neuronal m-type k^+ current

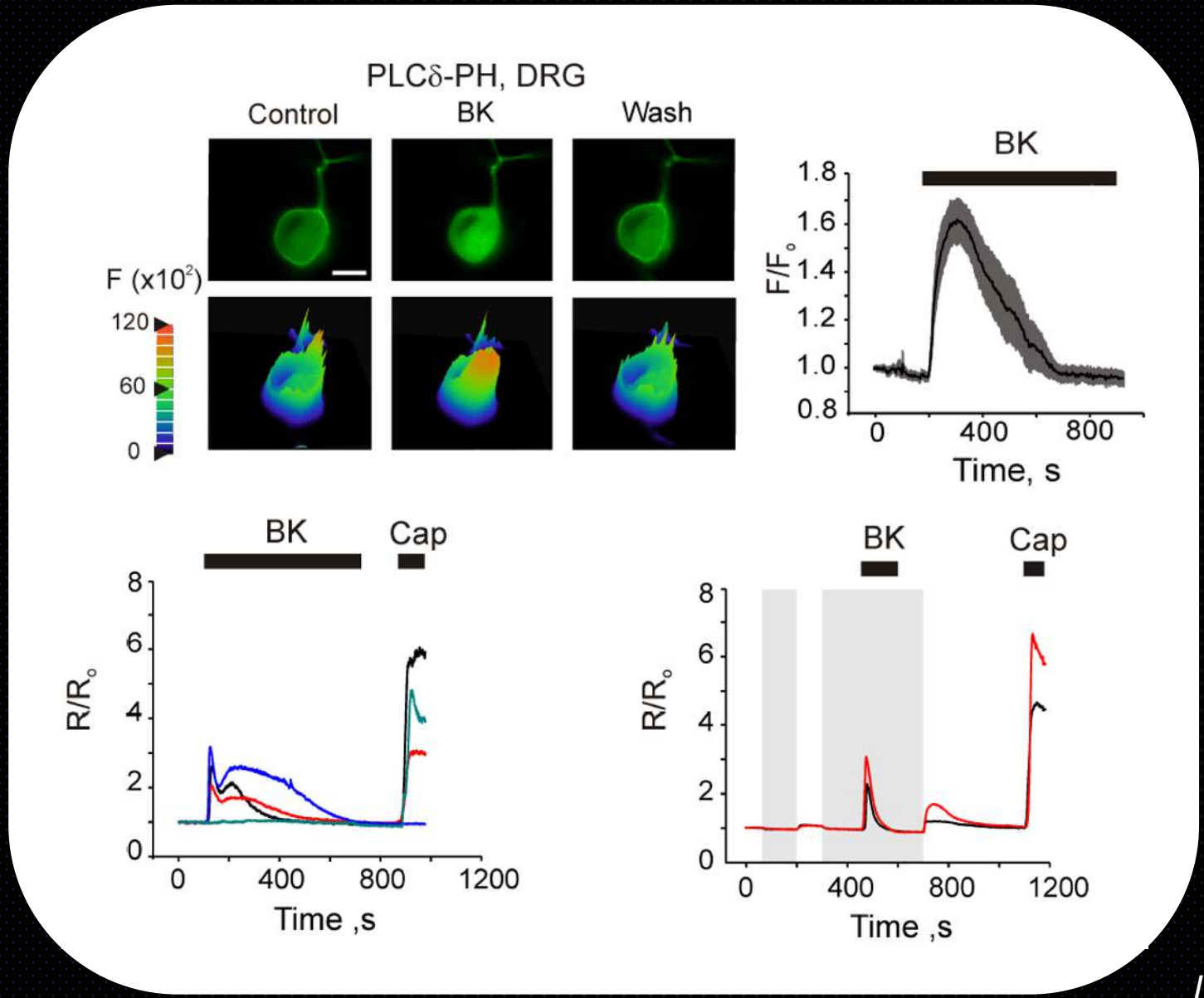




Working hypothesis for the role of M channel modulation in inflammatory pain

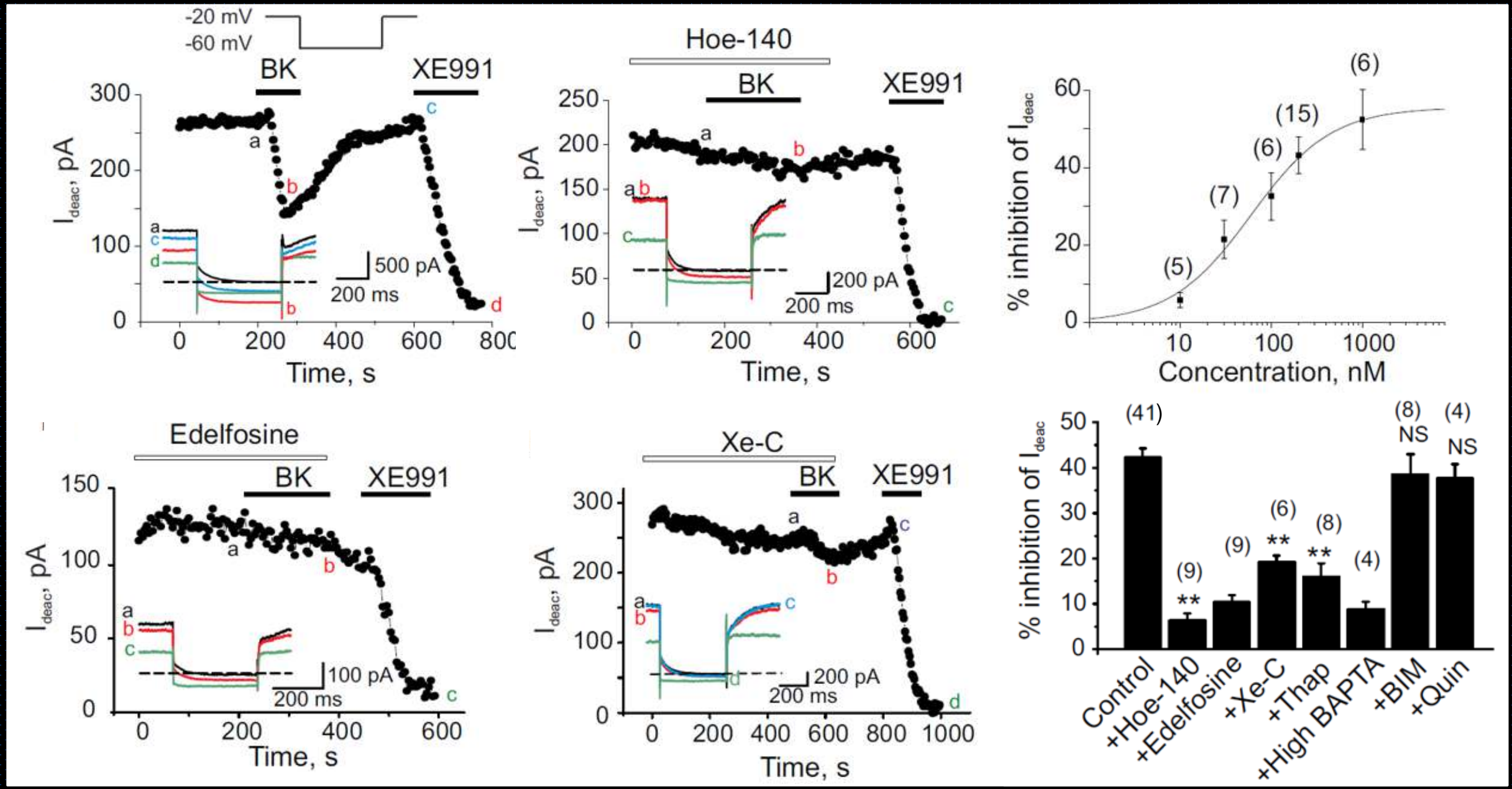


Bradykinin induces both PIP_2 hydrolysis and Ca^{2+} transients in DRG neurons



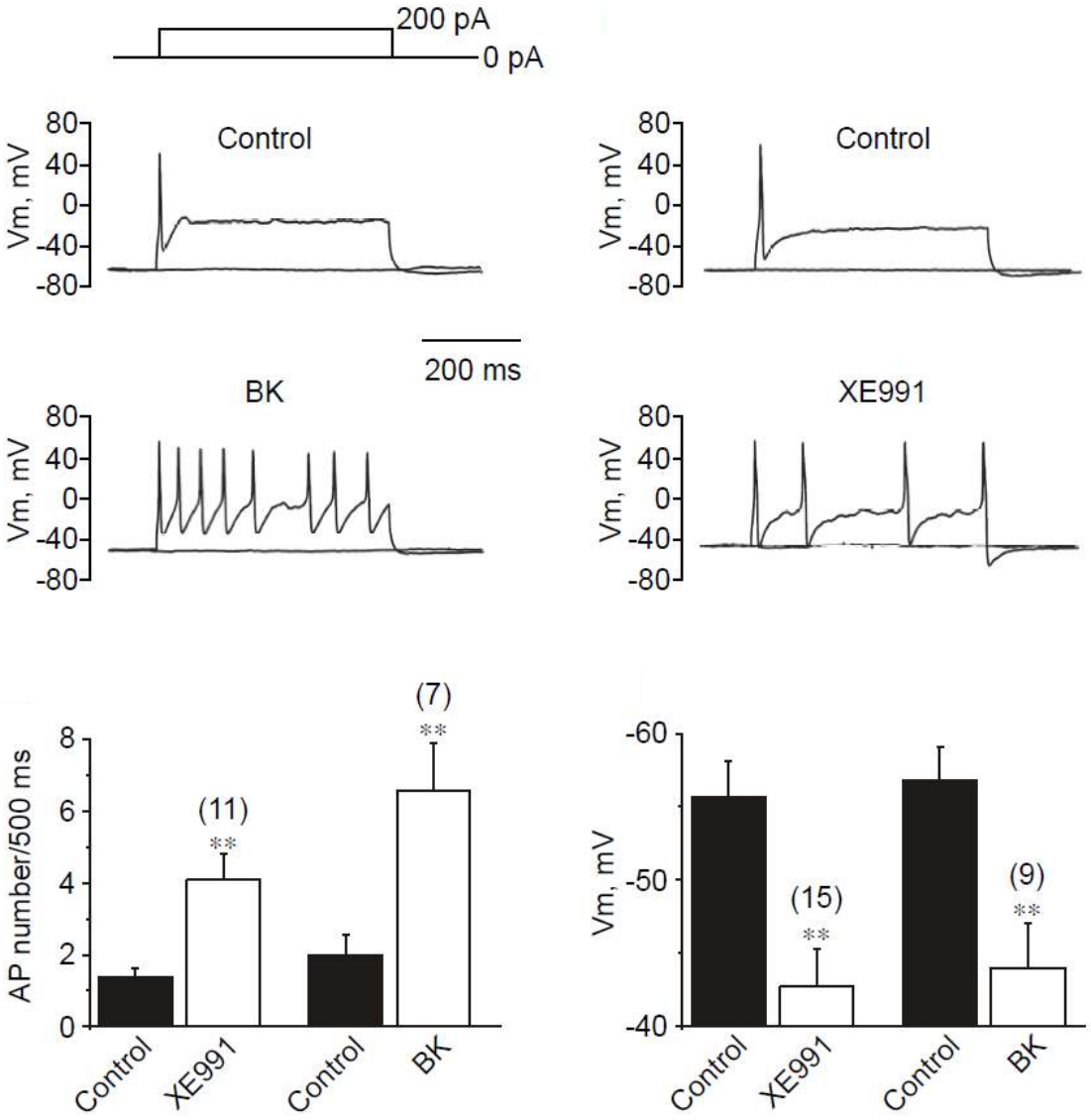
Liu et al (2010) J Clin Invest

Bradykinin strongly inhibits M current in DRG in a Ca^{2+}-dependent manner



Liu et al (2010) J Clin Invest

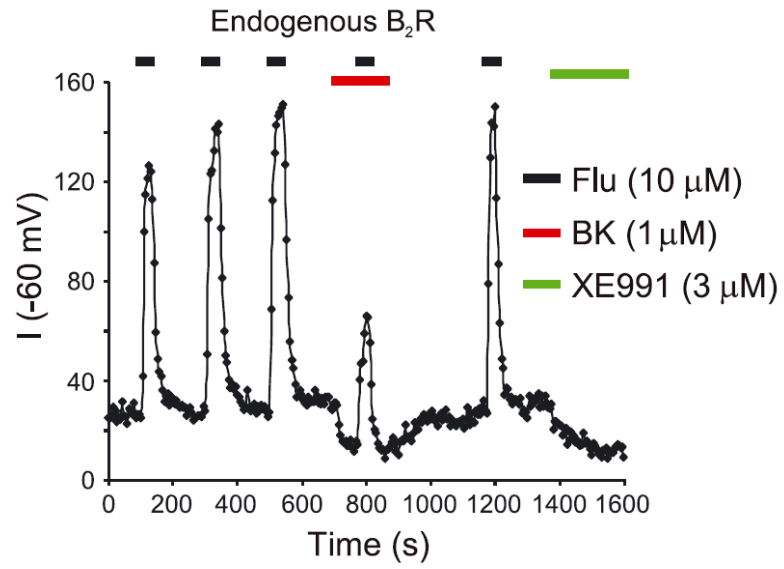
BK depolarizes and excites DRG neurons

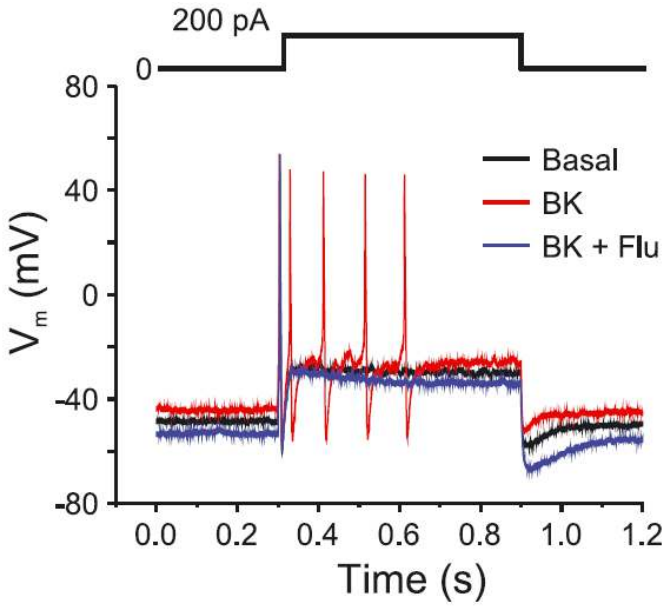


Liu et al (2010) J Clin Invest

Pharmacological M channel augmentation can offset BK-induced excitability

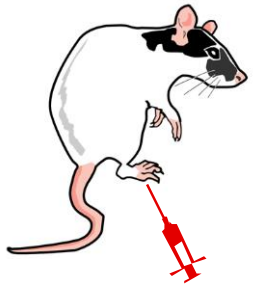
DRG neuron:





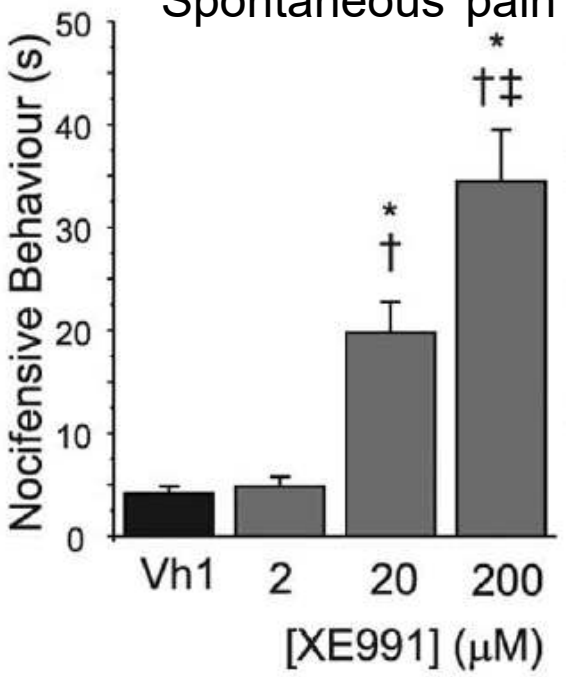
Linley et al. (2012) J Physiol

Peripheral M channel inhibition is painful while M channel enhancement is analgesic

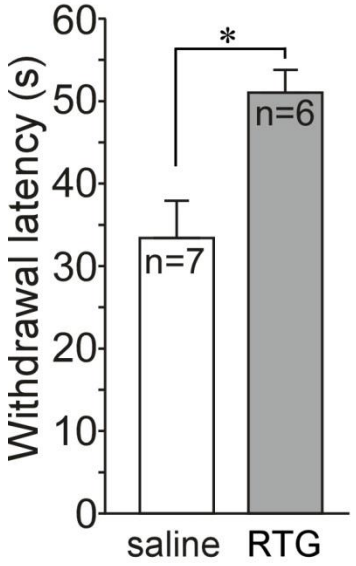


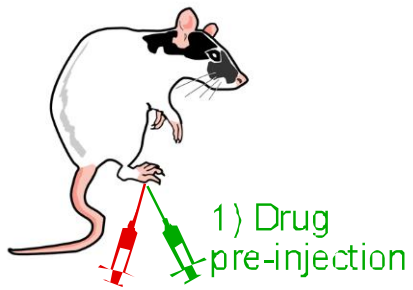
2) Painful stimulus

‘Spontaneous’ pain

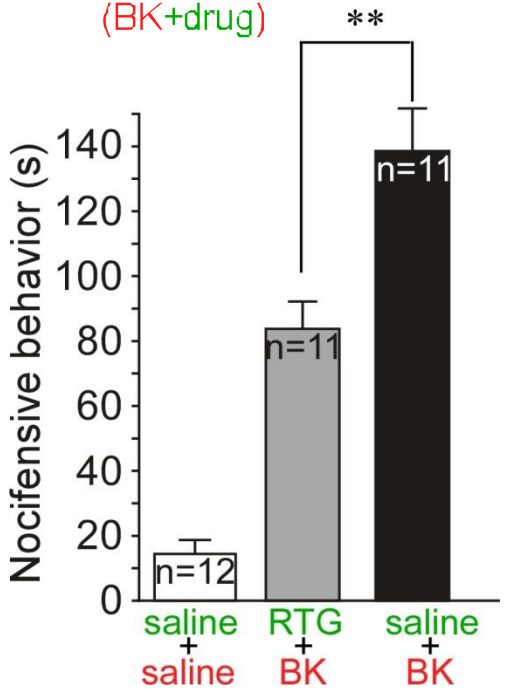


Heat sensitivity



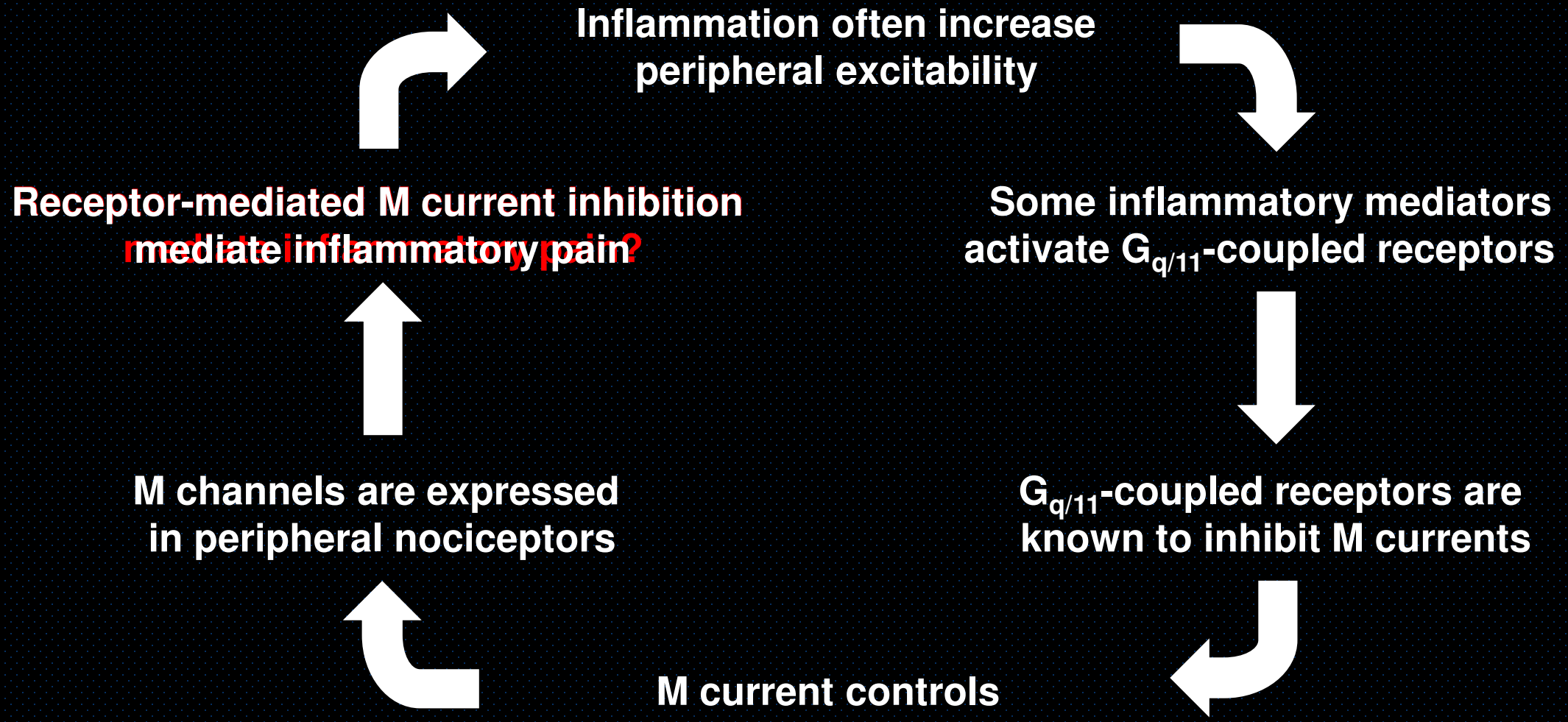


2) Painful stimulus
(BK+drug)



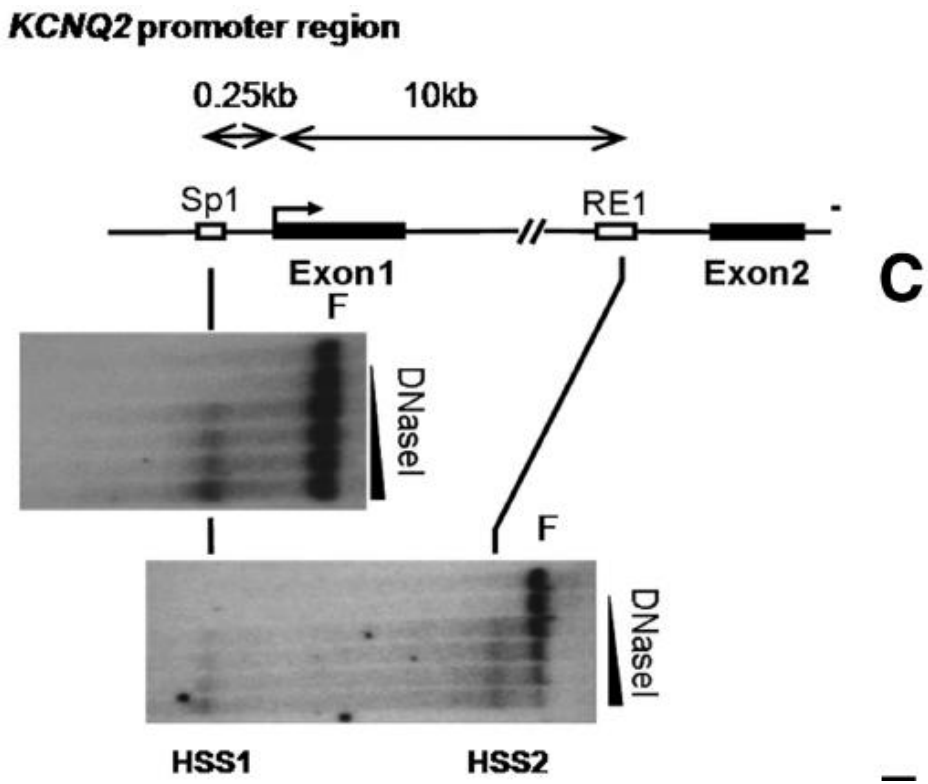
Linley et al. (2008) J Nurosci; Liu et al. (2010) JCI; Huang et al. (2016) ARS

Working hypothesis for the role of M channel modulation in inflammatory pain



Role of M channels in neuropathic pain

KCNQ gene expression is regulated by the transcription factors sp1 and REST



C

KCNQ2 Sp1 region

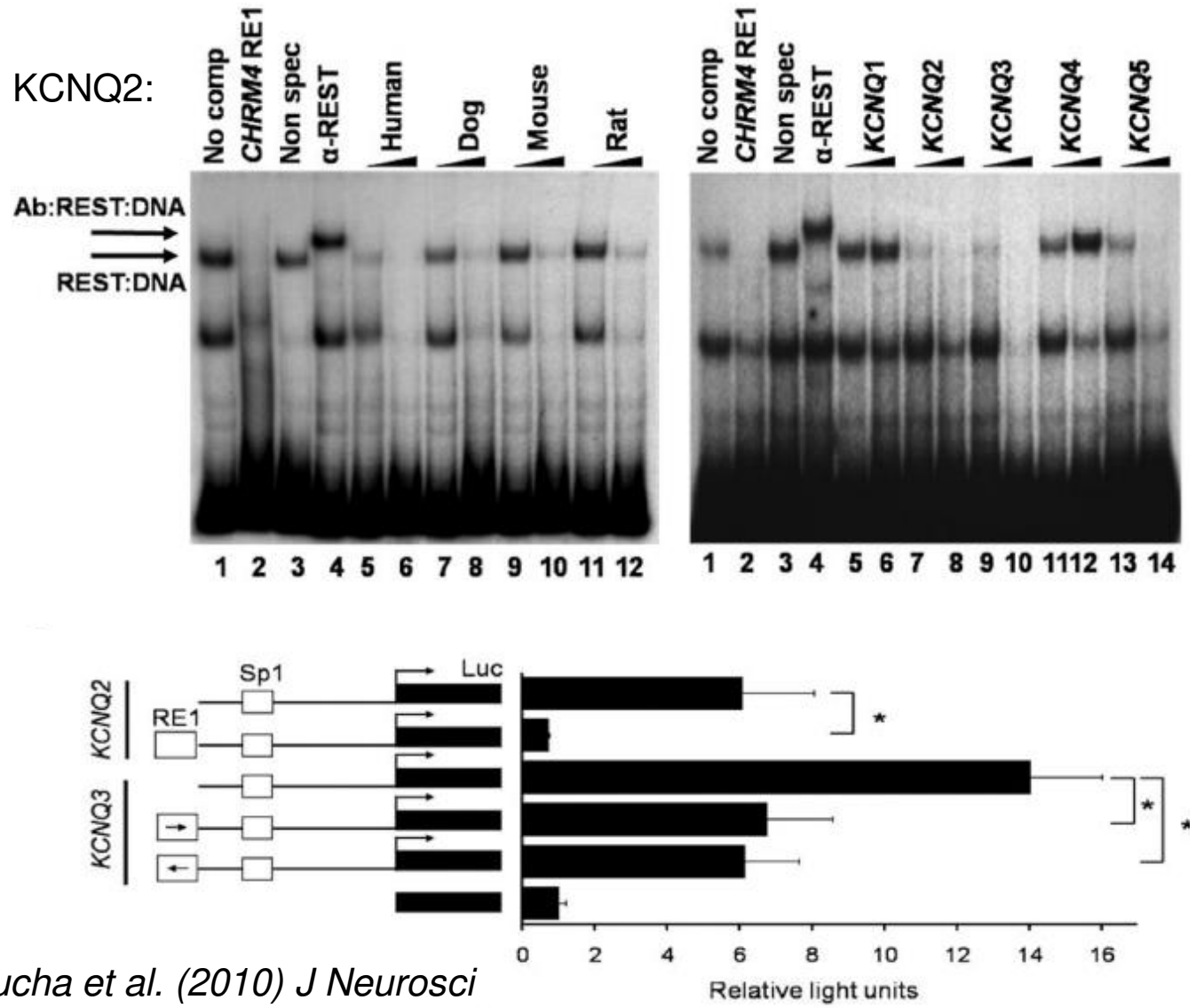
Consensus	GrGGCrGGGs
Human	GGGGTTAACGCGGGGCGGGGCGAGGCGGCG
Mouse	TAGGGTTAAGGCGGGCGGGGCGGGGCGGCG
Rat	TAGGGTTAAGGCGGGCGTGGGGCGGGGGCG

KCNQ2 RE1 region

Consensus	nTyAGmrCCnnrGmsAG
Human	GCTCCTGGTCAGGACCATGGCCAGCACCCC
Chimp	GCTCCTGGTCAGGACCATGGCCAGCACCCC
Rhesus	GCTCCTGGTCAGGACCACGGCCAGCA-CCC
Mouse	ACTTGAGTCCAGGACCATGGTCAGCACCAC
Rat	ATTTGCGTCCAGGACCATGGTCAGCGCCAC
Dog	CCTGCTGCTCAGGACCACGGCCAGCGCCTC
Cow	GTTCCTGATCAGGACCACGGCCAGCACCCC
Elephant	GCTCGTGTTCAGCACCAAGGCCAGCGCCAA

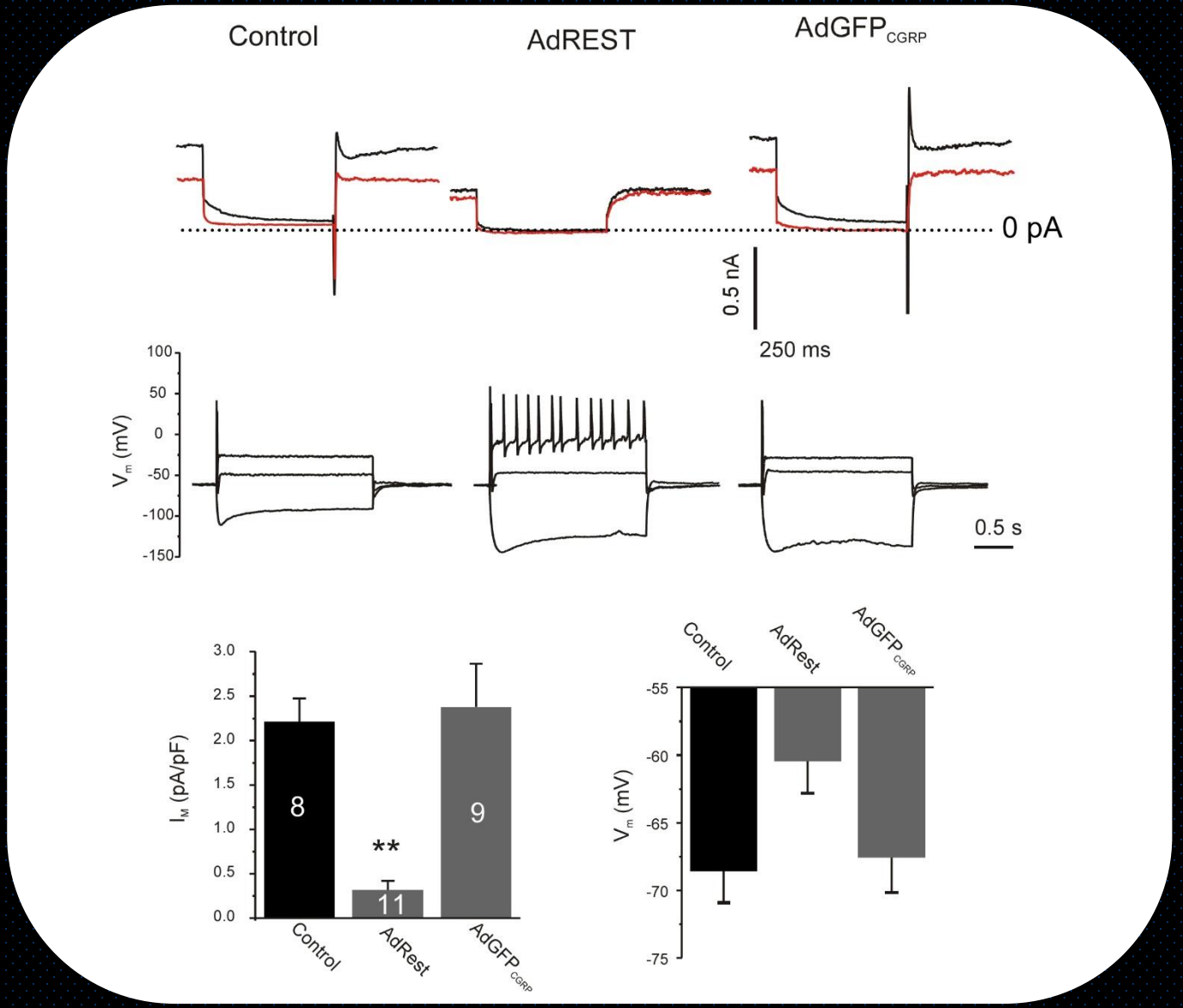
Mucha et al. (2010) J Neurosci

REST can bind to KCNQ genes and suppress its transcription



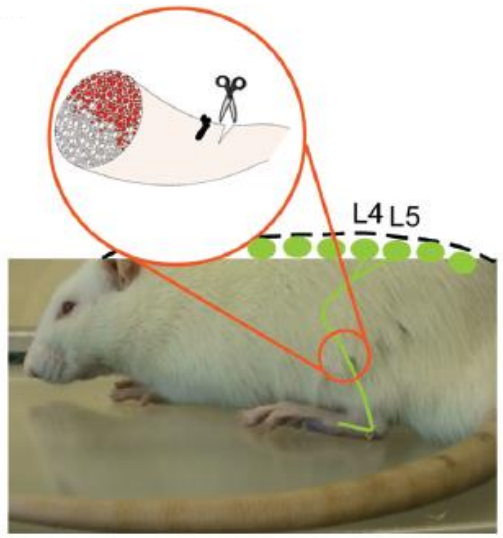
Mucha et al. (2010) J Neurosci

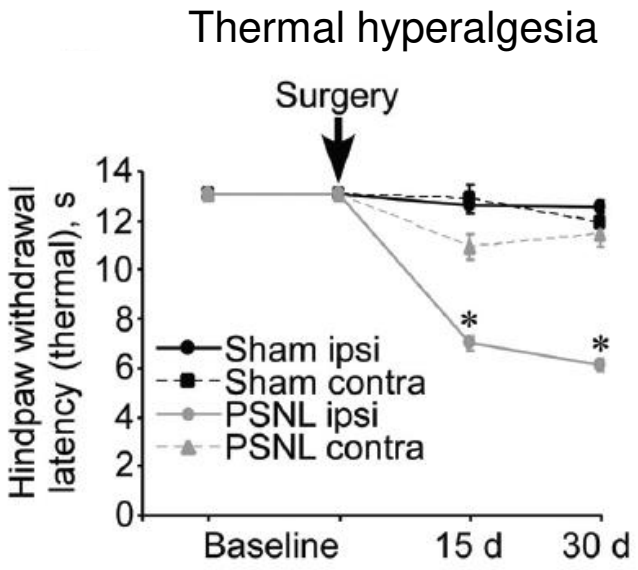
Overexpression of REST in DRG neurons decreases tonic M current density and results in overexcitable neurons

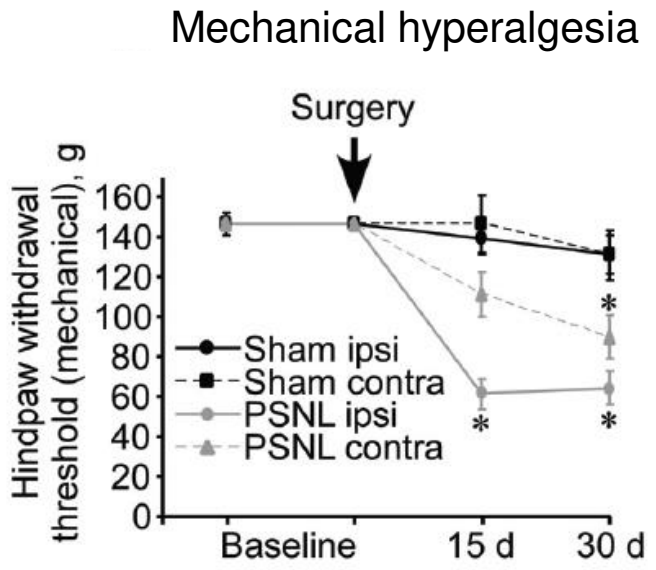


Mucha et al. (2010) J ***Neurosci***

We used Partial Sciatic Nerve Lesion model for neuropathic injury:

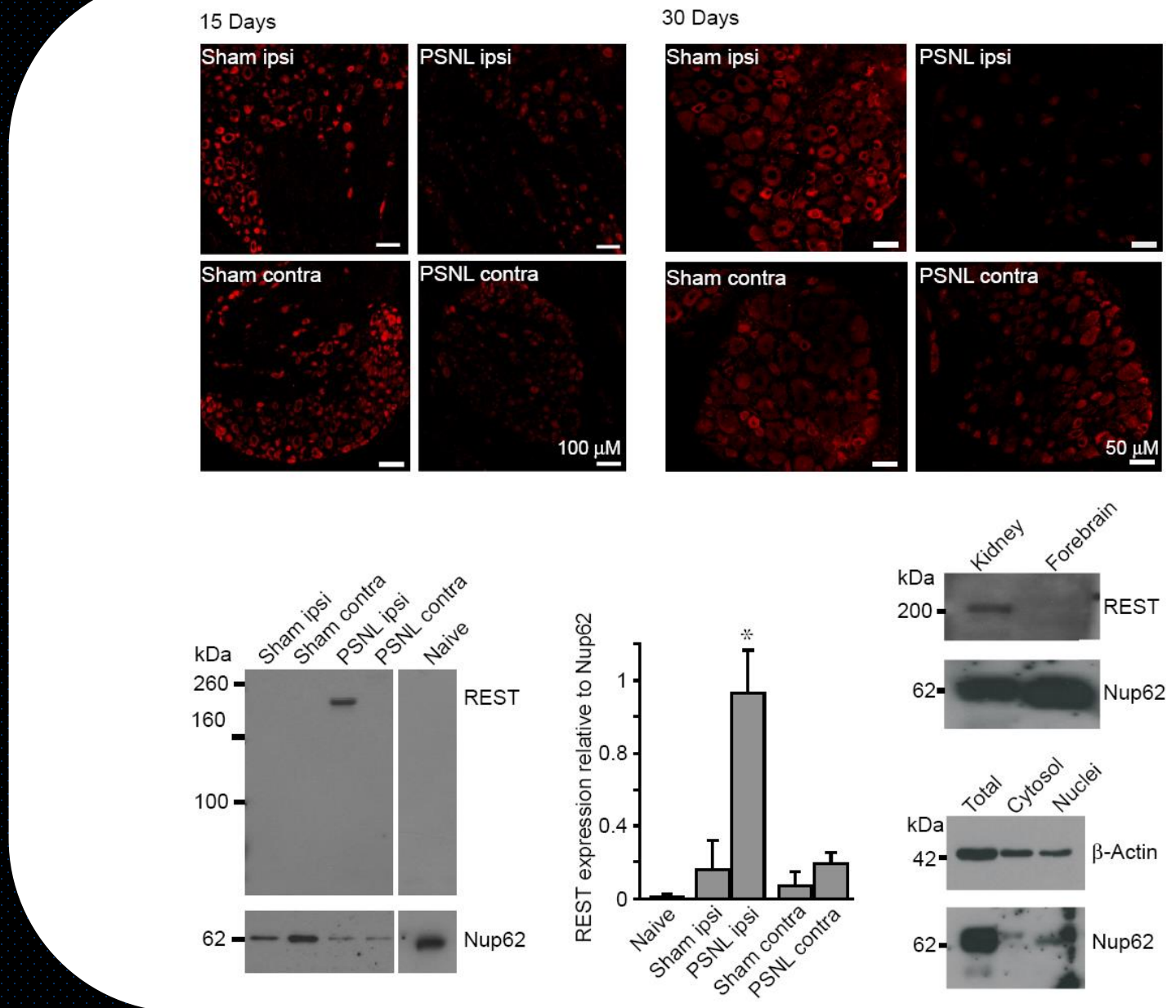






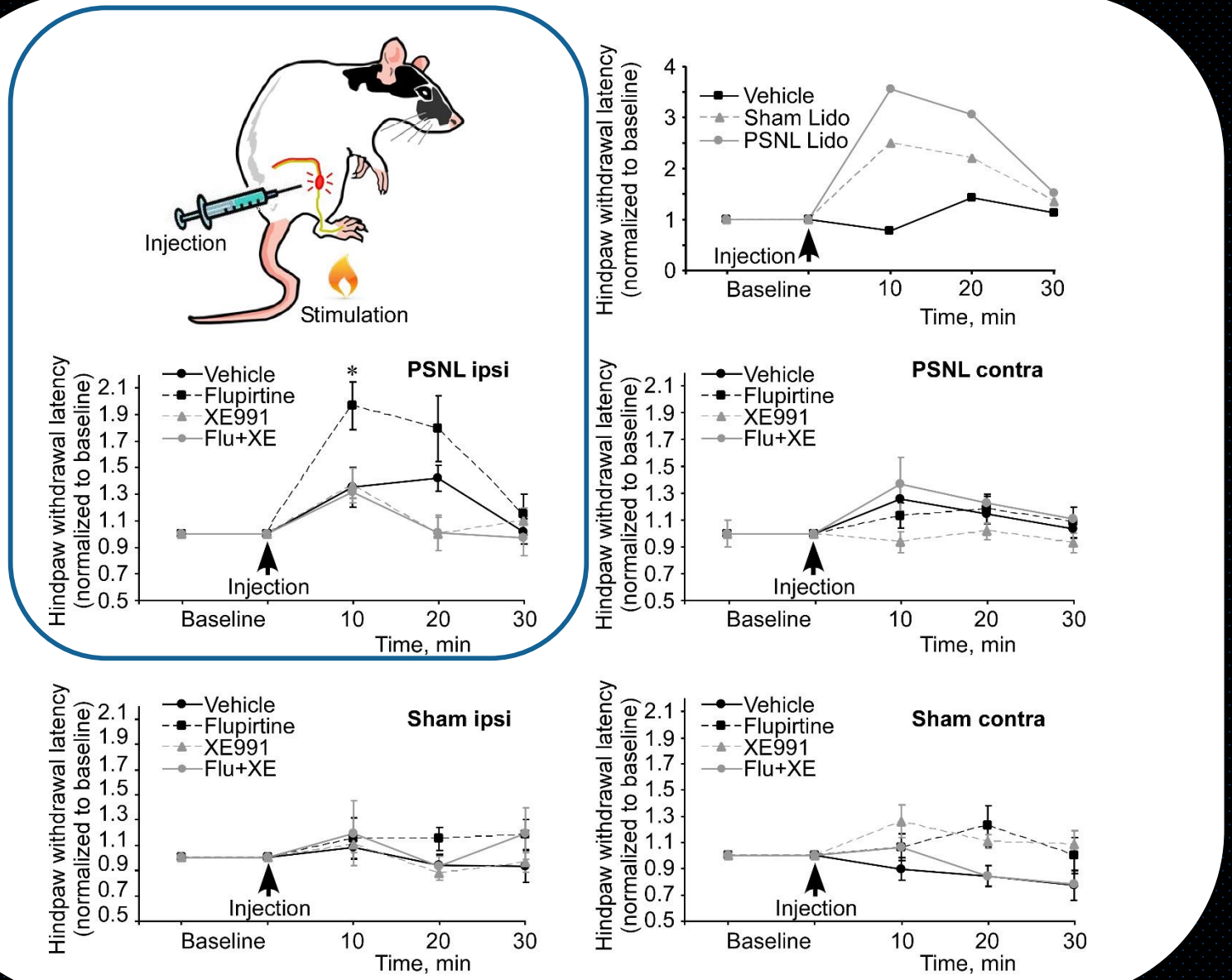
Rose et al. (2011) PAIN

Expression of Kv7.2 and REST proteins in DRG show reciprocal changes after neuropathic injury



Rose et al. (2011) PAIN

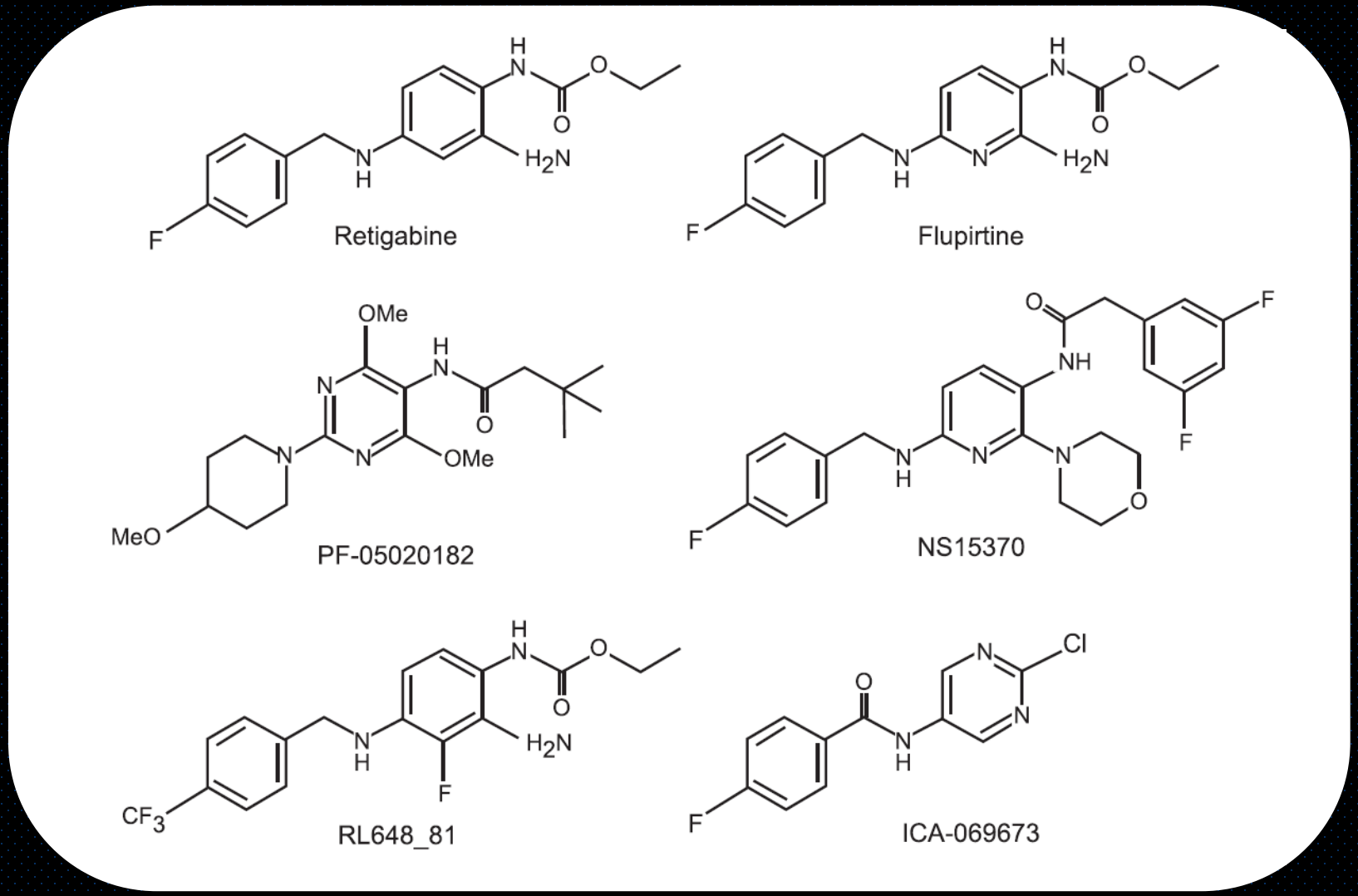
Perisciatic nerve injection of M channel opener alleviated thermal hyperalgesia produced by PSNL



Rose et al. (2011) PAIN

M channel openers as prospective analgesics and where within the nervous system might they act?

M channel openers are prospective antiepileptic drugs and analgesics



Du et al. BJP 2017

Hayashi *et al. Molecular Pain* 2014, **10**:15
http://www.molecularpain.com/content/10/1/15

MOLECULAR PAIN

RESEARCH Open Access

Activation of peripheral KCNQ channels attenuates inflammatory pain

Hiroki Hayashi, Masashi Iwata, Noboru Tsuchimori* and Tatsumi Matsumoto

Activation of peripheral KCNQ channels relieves gout pain.

Basic Pharmacology

Pain. POST ACCEPTANCE, 12 February 2015
Zheng, Yueming; Xu, Haiyan; Zhan, Li; Zhou, Xindi; Chen, Xueqin; Gao, Zhaobing

Research Article

MOLECULAR PAIN

Molecular Pain
Volume 13: 1–16

DOI: 10.1177/1744806917709371
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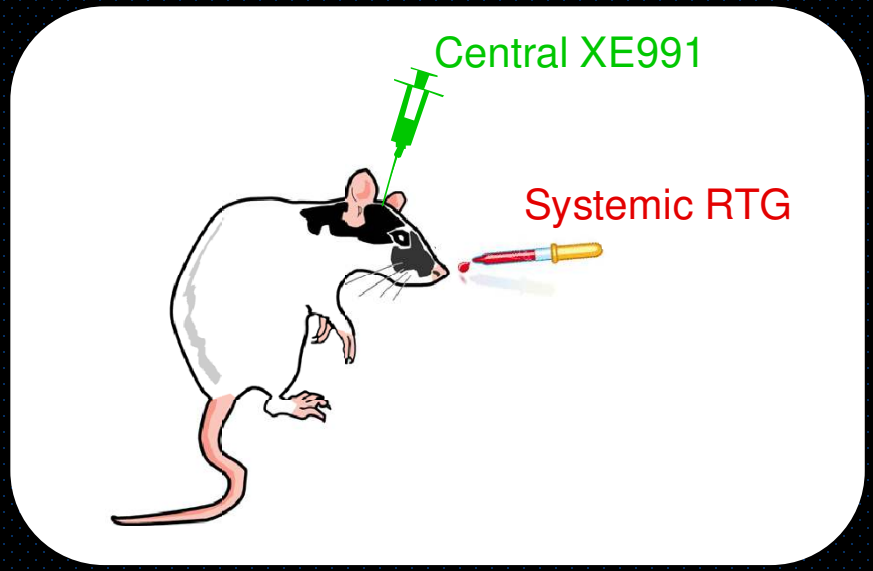
SAGE

Peripheral K_V7 channels regulate visceral sensory function in mouse and human colon

Madusha Peiris[1*], James RF Hockley[2*], David E Reed[3], Ewan St. John Smith[2], David C Bulmer[1] and L Ashley Blackshaw[1]

Hayashi et al:

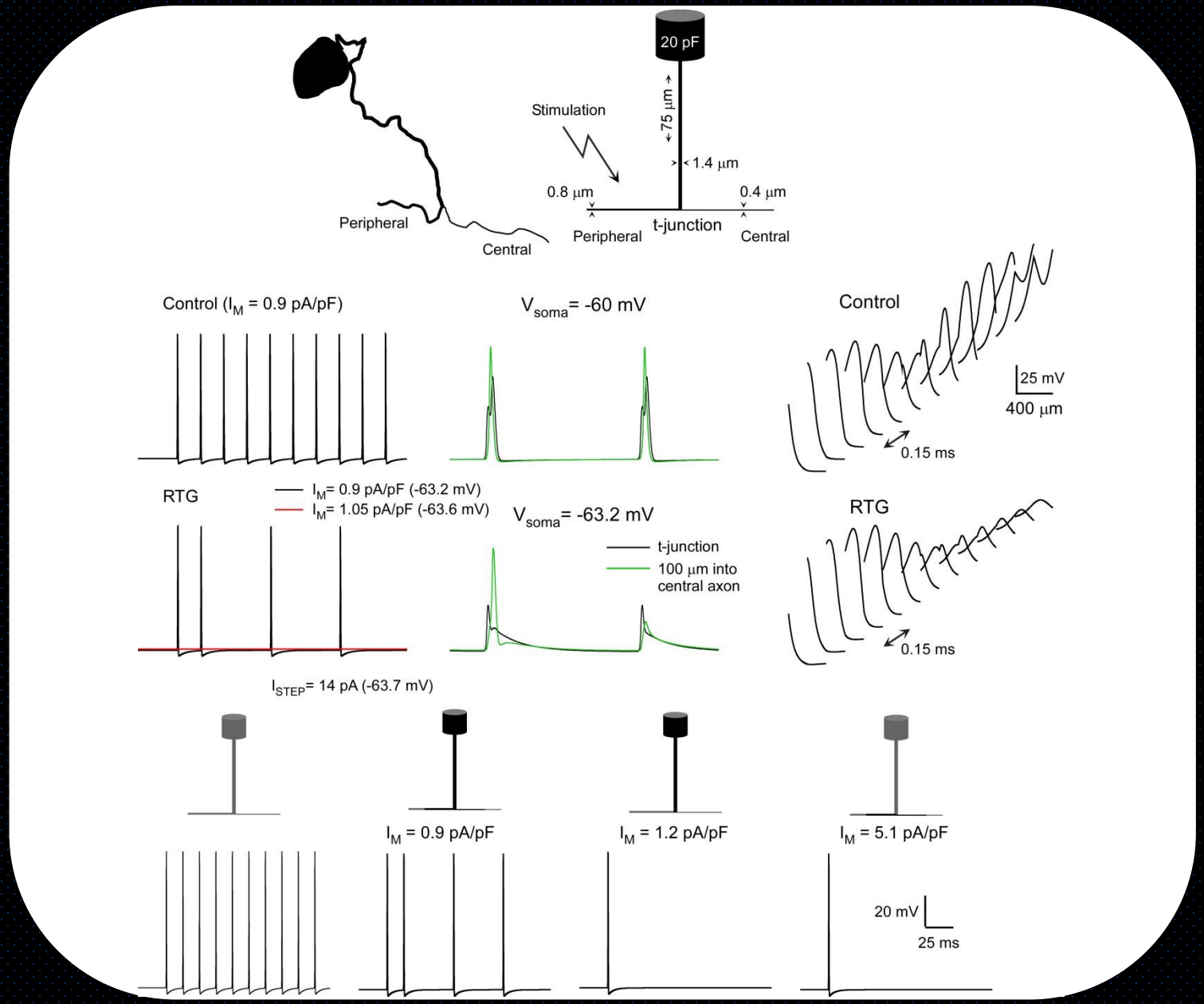


Oral RTG:

Reversibility by i.c.v. XE991:

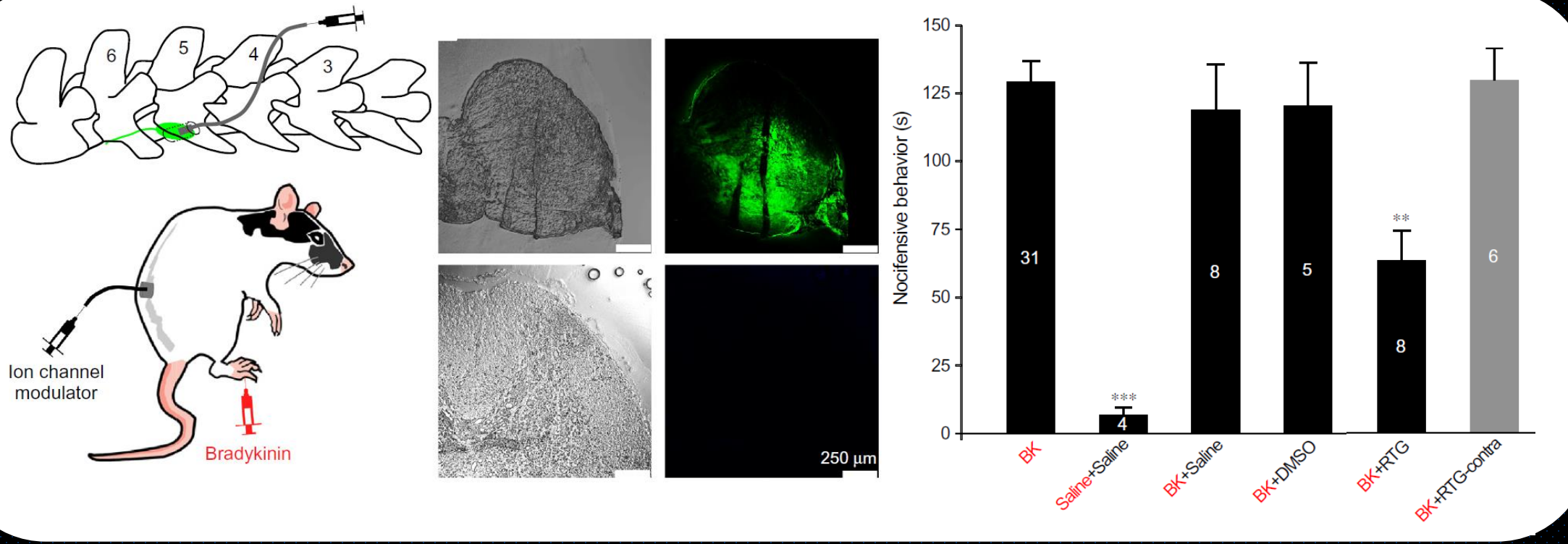
- anticonvulsant effect……..... ✓
- impaired motor coordination…… ✓
- reduced exploratory behavior…….. ✓
- analgesic effect…….. X

Axonal bifurcation (T-junction) is a site of reduced safety factor for AP propagation



Du et al. (2014) PAIN
Sundt, Gamper & Jaffe (2015) J Neurophysiol

Focal application of RTG via DRG cannula alleviates peripheral pain

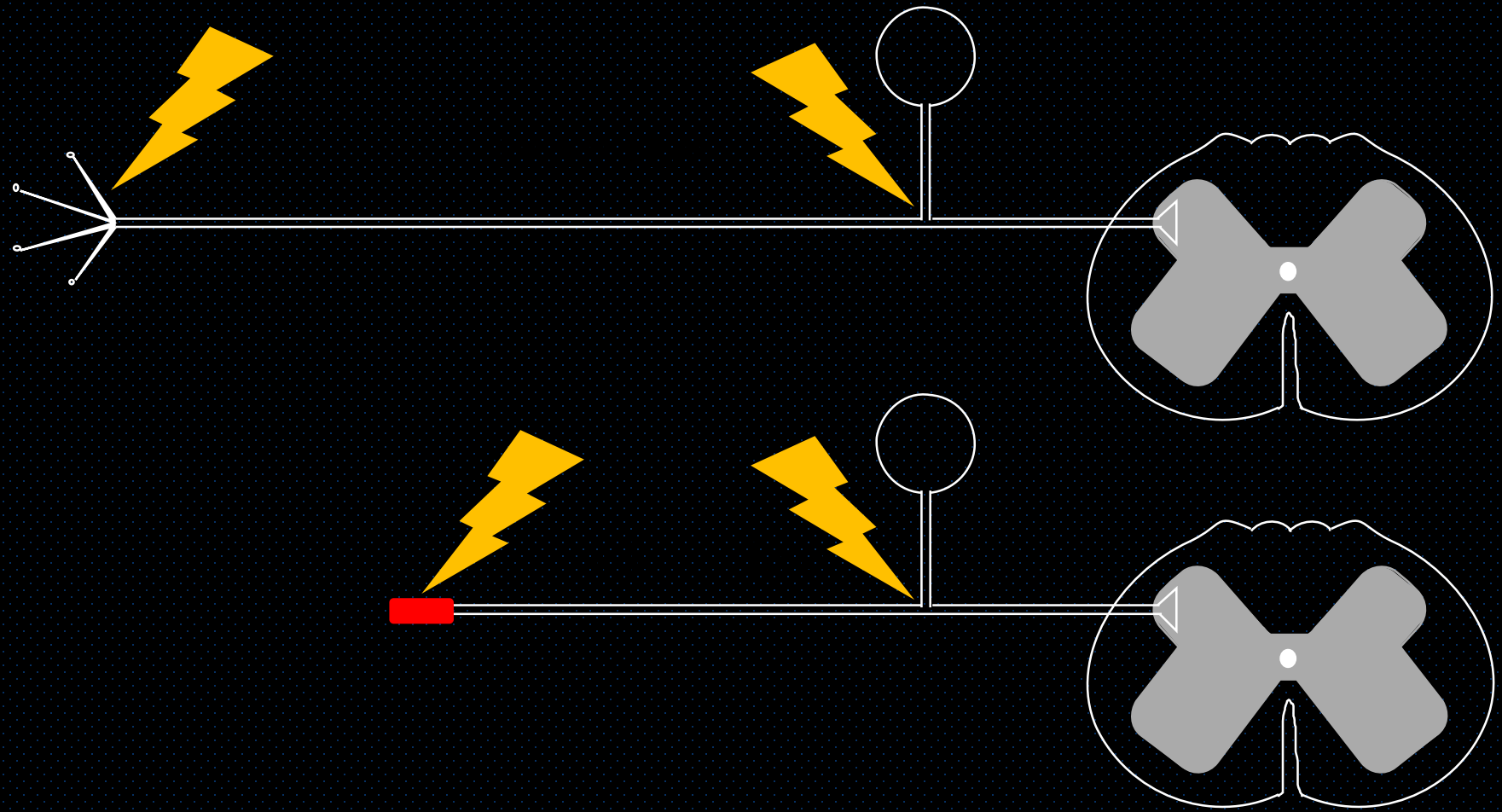


Du et al. (2014) PAIN

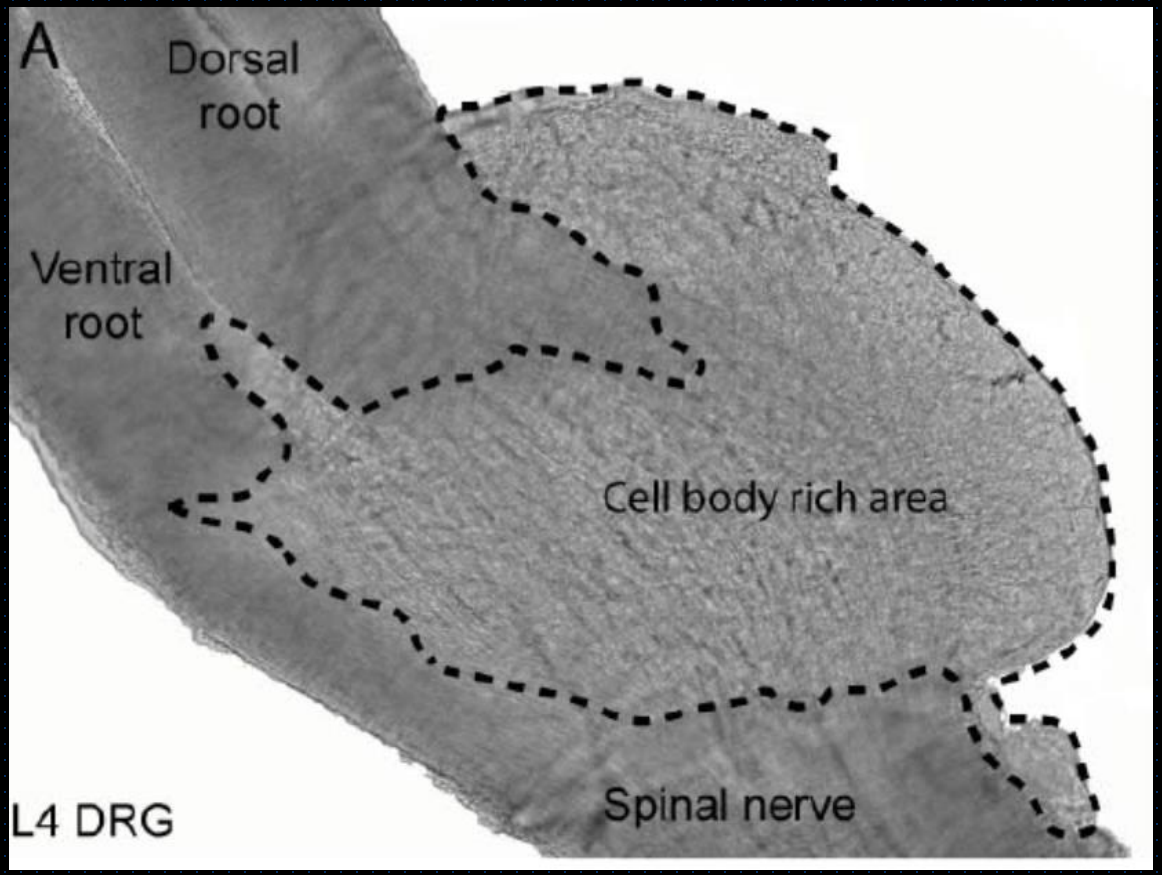
My current hypothesis:

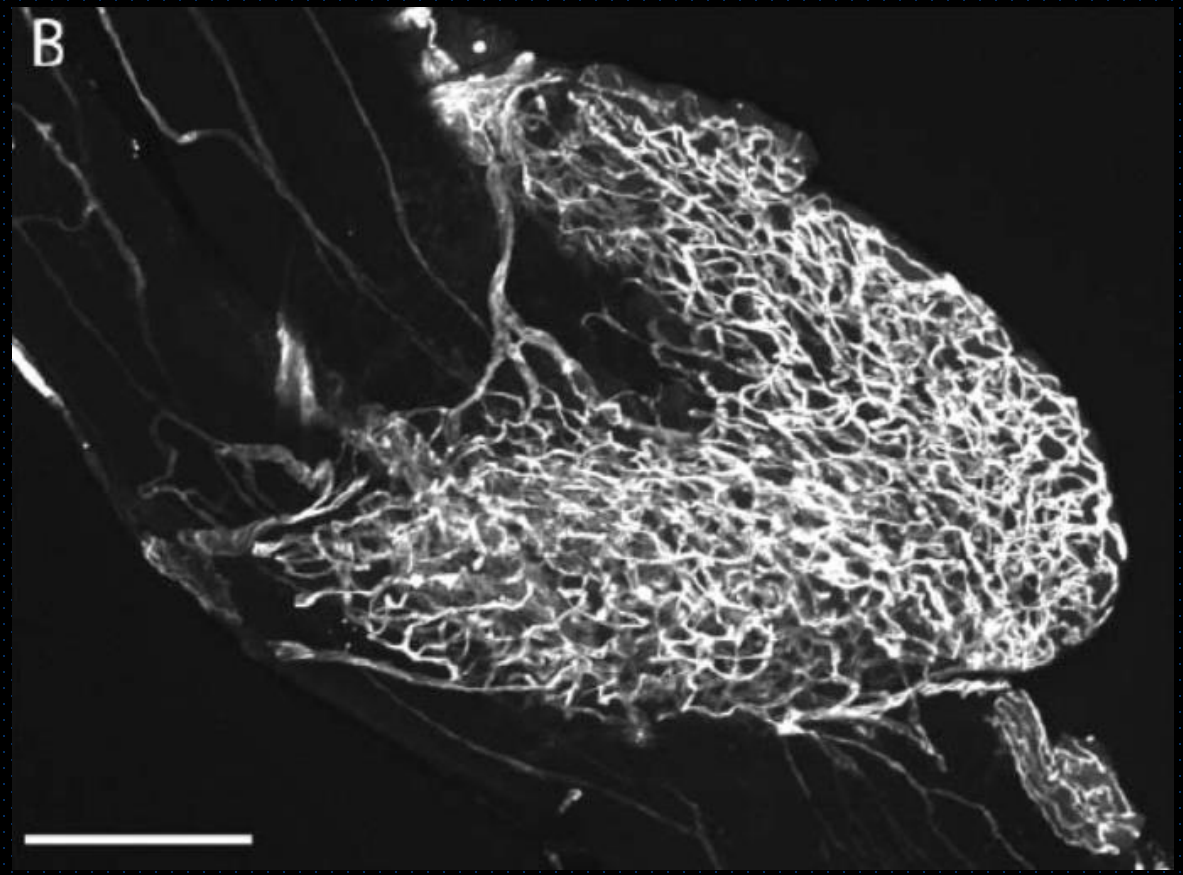
within peripheral somatosensory system M channel openers are most efficacious

- at sites of AP generation
- at T-junctions



NOT ONLY DRG IS NOT PROTECTED BY THE BBB/BNB BUT IT IS SUPPLIED BY AN EXCEPTIONALLY DENSE VASCULAR NETWORK





Mantyh et al (2008) Mol Pain

University of Leeds

John Linley
Xin Jin
Lezanne Ooi
Shihab Shah
Sylvain Gigout
Haixia Gao
Rosmaliza Ramli
Aurelian Bolliat
Alexandra Gerghina
Hannah Kirton
Ewa Jaworska
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UTHSCA San Antonio

Mark Shapiro
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UTSA San Antonio

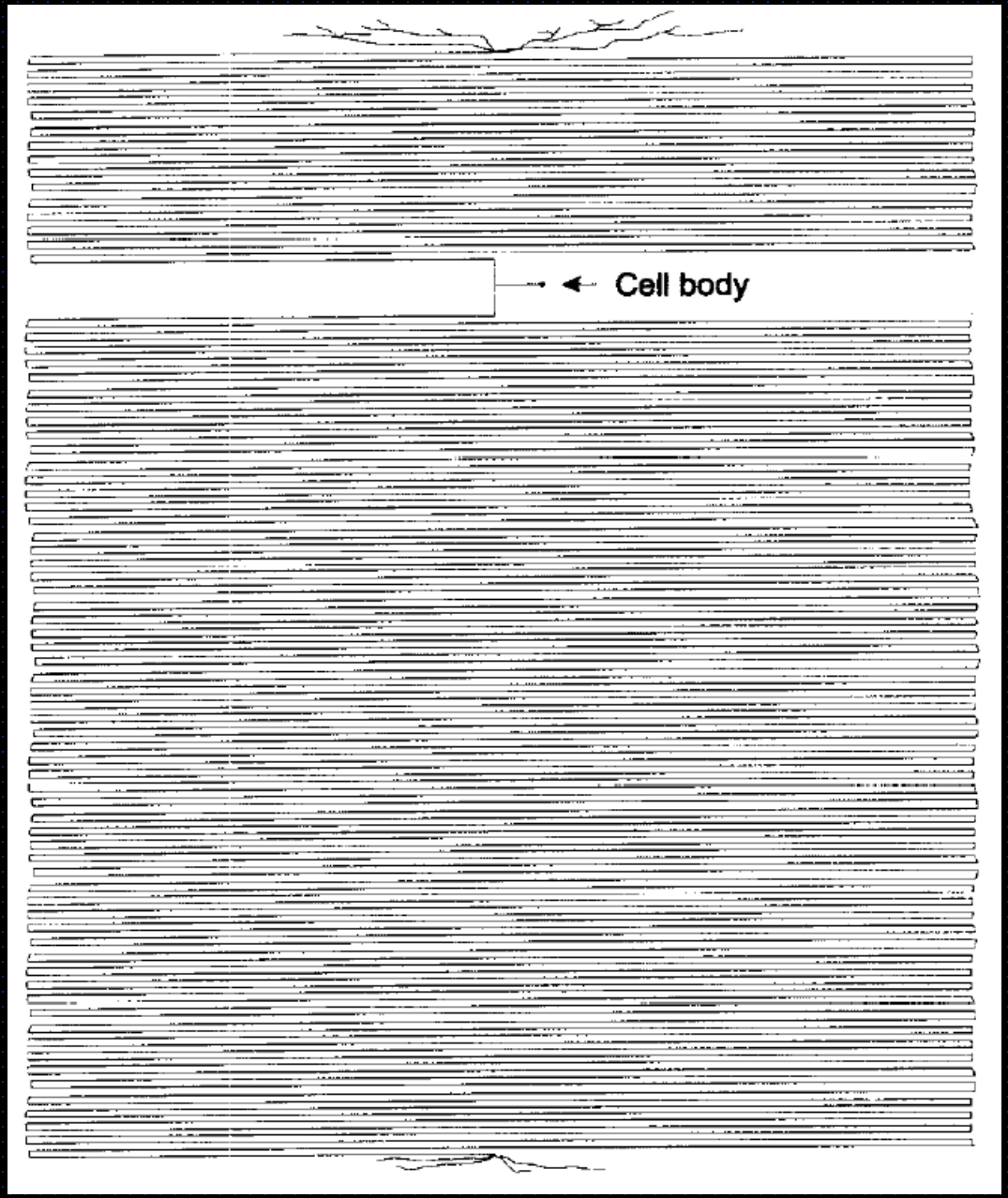
David Jaffe

Hebei Medical University, China

Hailin Zhang

Boyi Liu
Xiaona Du
Han Hao
Fan Zhang
Dongyang Huang
Sha Huang
Yuehui Yang
Caixue Wang
Jinlong Qi
Liu Yani
Huiran Zhang
Zhanfeng Jia
Ce Liang

PERIPHERAL SOMATOSENSORY NEURONS ARE 'SPECIAL'



Marshall Devor Pain 1999