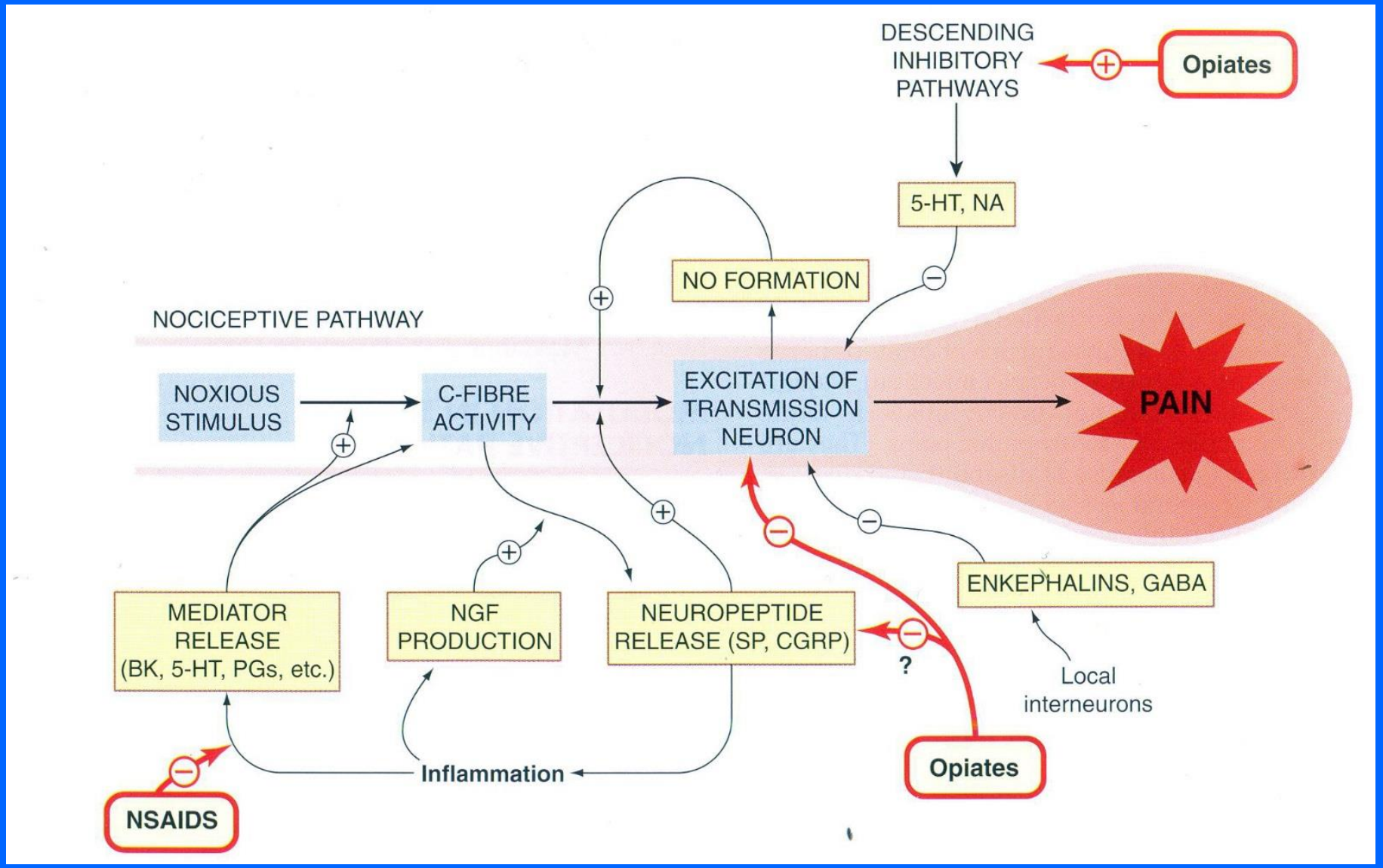
Precision Medicine & Ion Channel Retreat 2016

Substance P: an odd player in a painful game

Nikita Gamper

Substance P is one of the main excitatory transmitters in the spinal cord



Rang & Dale Pharmacology

−11.6 mm, $p = 0.664$) nor for change in ratings of different pain symptoms (touch- or pressure-evoked pain, pain paroxysms, steady burning or deep aching pain) ($p = 0.169$–0.834).

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Keywords: NK_1-receptor antagonist; Painful diabetic neuropathy; Treatment

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Activation of Neurokinin-1 Receptors Increases the Excitability of Guinea Pig Dorsal Root Ganglion Cells

Xiulin Zhang, Claudio Pietra, Emanuela Lovati, and William C. de Groat

PNAS

An antinociceptive role for substance P in acid-induced chronic muscle pain

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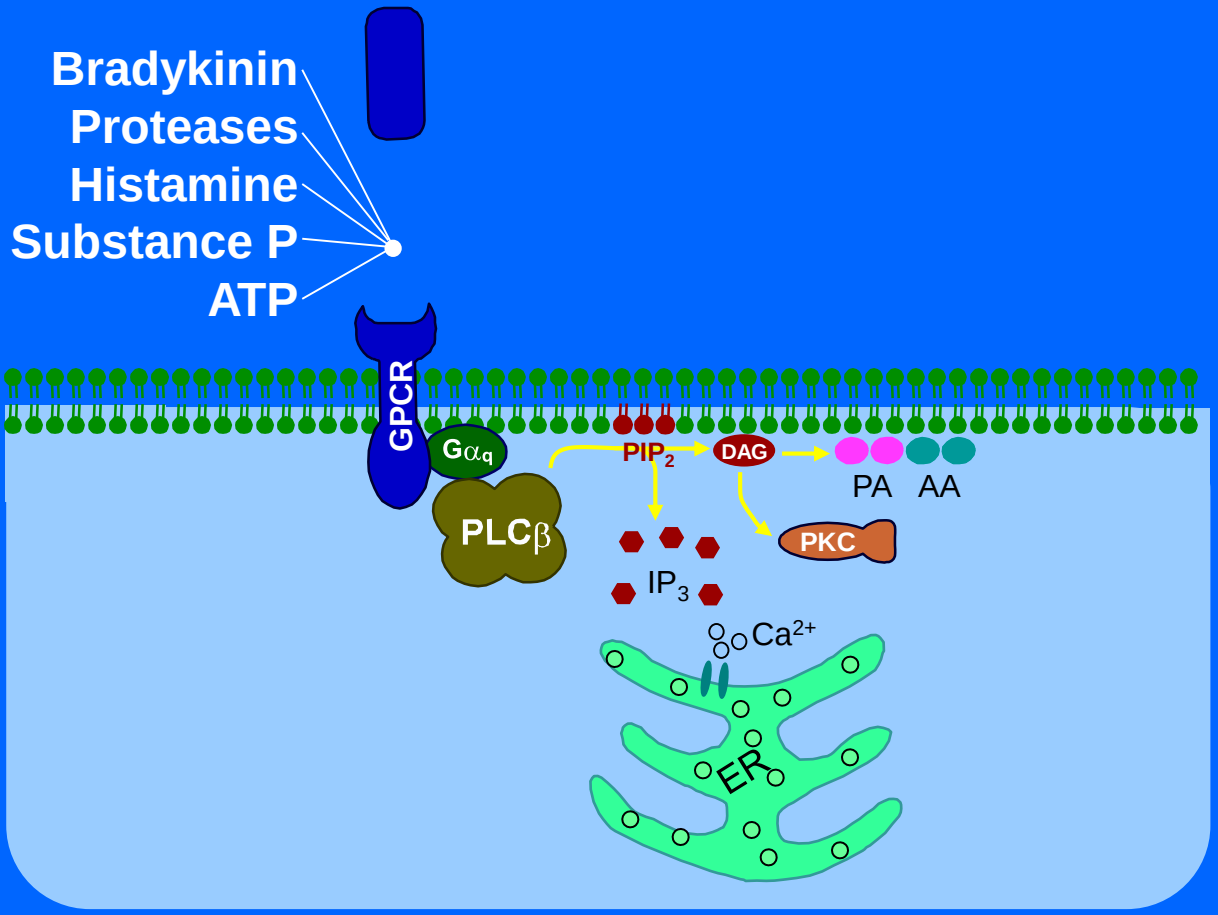
Edited by Tomas G. M. Hökfelt, Karolinska Institutet, Stockholm, Sweden, and approved October 25, 2011 (received for review June 2, 2011)

Basal and activity-induced release of substance P from primary afferent fibres in NK_1 receptor knockout mice: evidence for negative feedback

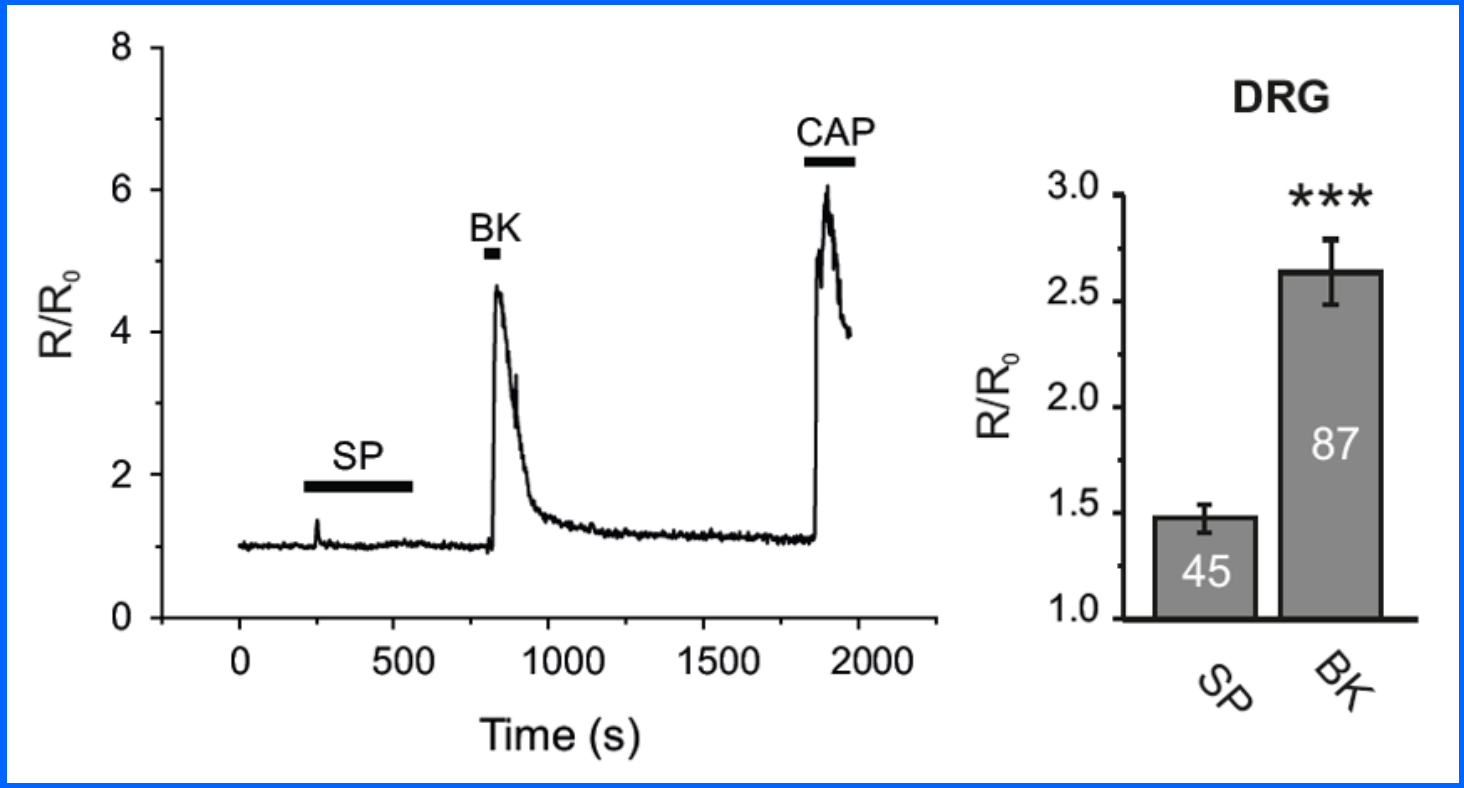
Isobel J. Lever [a], Andrew D. Grant [b], Sophie Pezet [a], Norma P. Gerard [c], Susan D. Brain [b], Marzia Malcangio [a,*]

Tachykinin receptors belong to $G_{q/11}$- type of GPCR



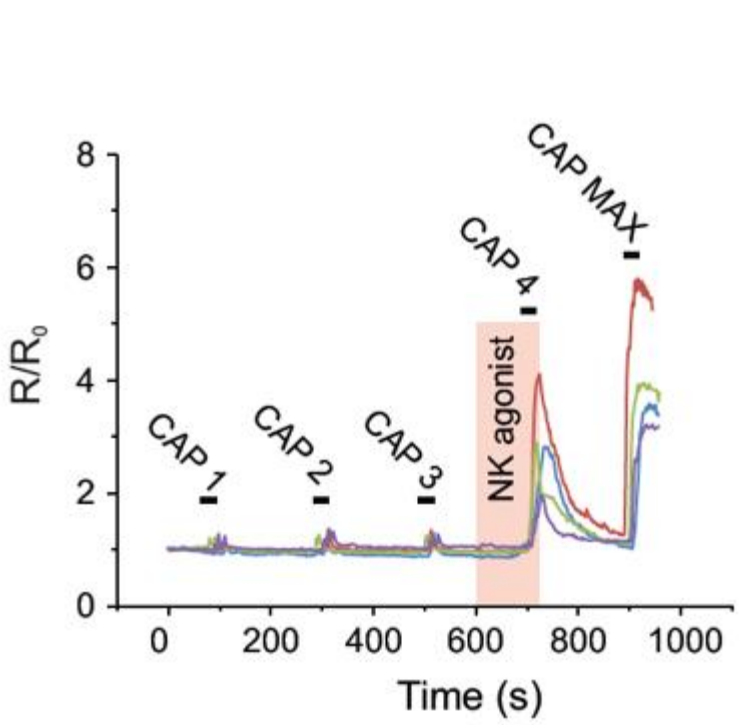
NK receptors couple poorly to Ca^{2+} signaling in DRG neurons

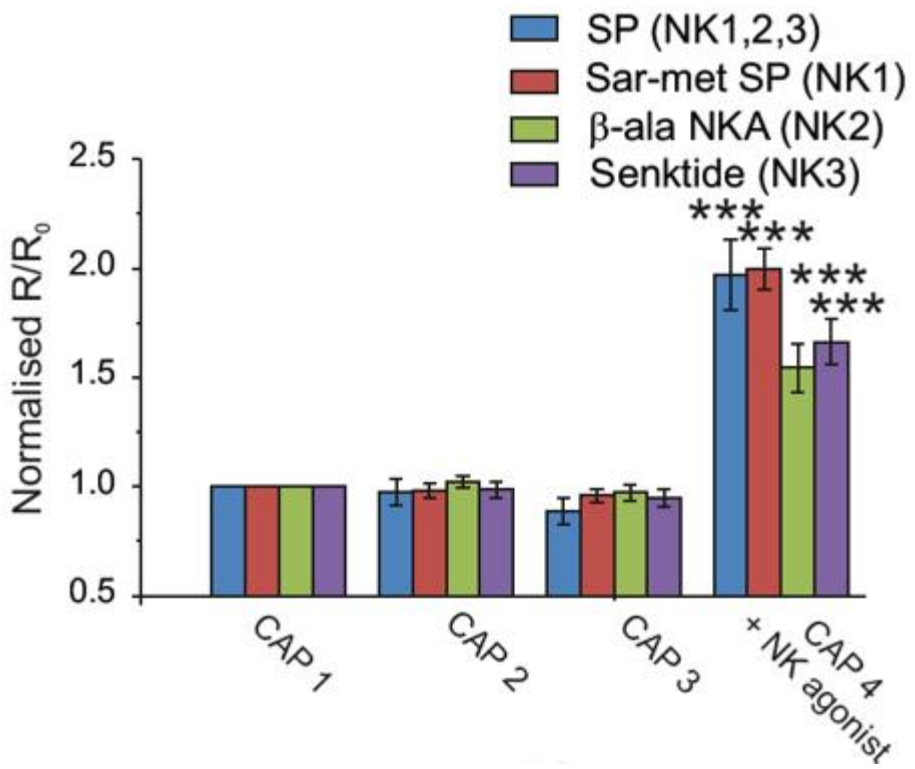
Are these expressed, are they functional?



Linley et al PNAS 2012

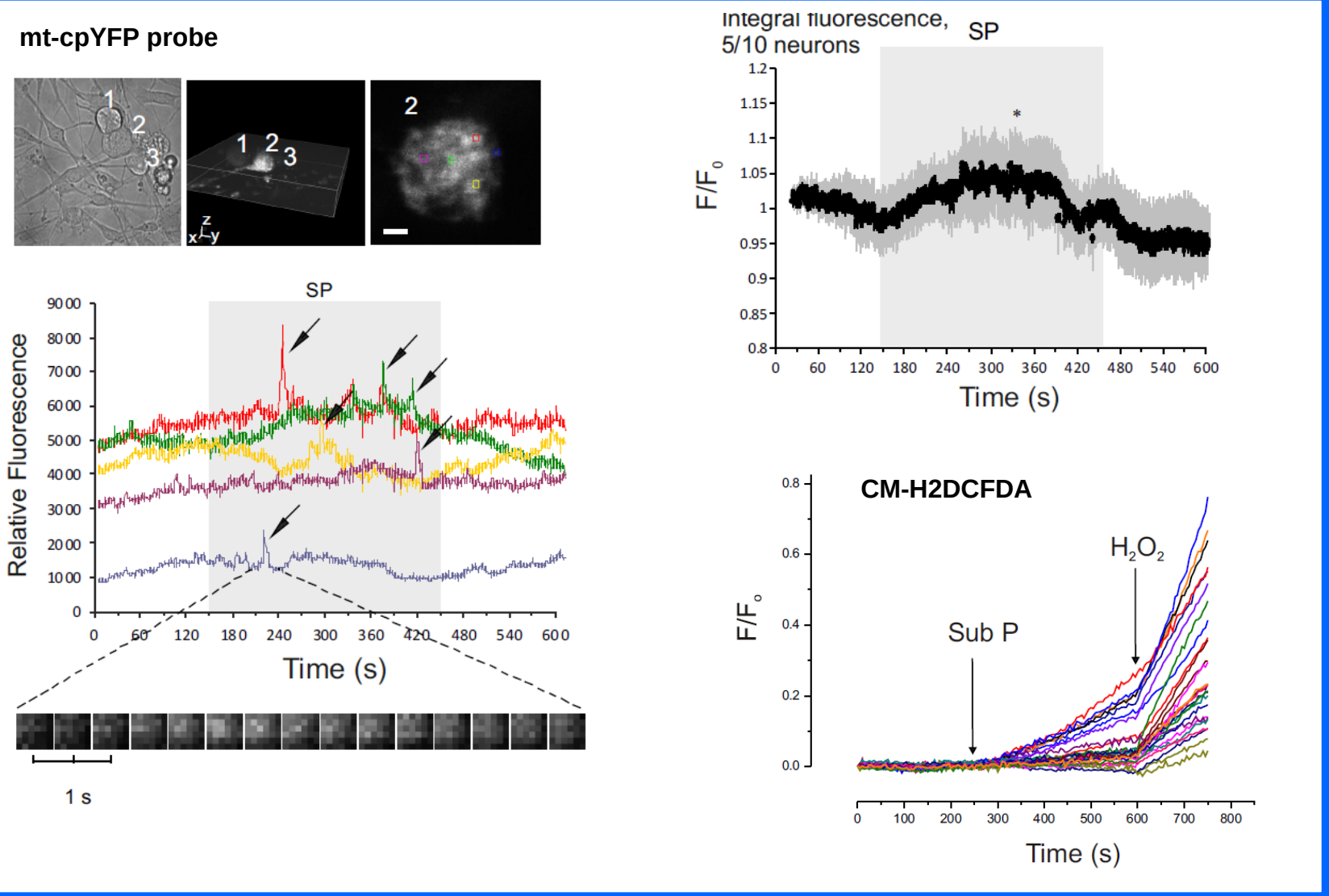
DRG neurons express functional receptors for substance P (NK1-3)





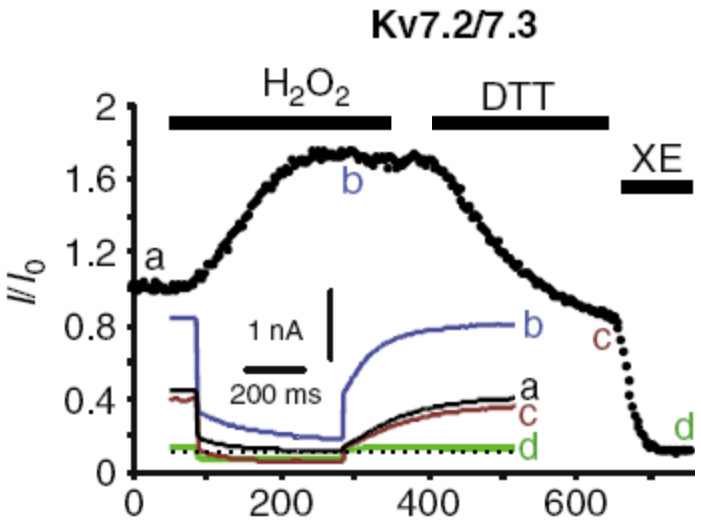
Linley et al PNAS 2012

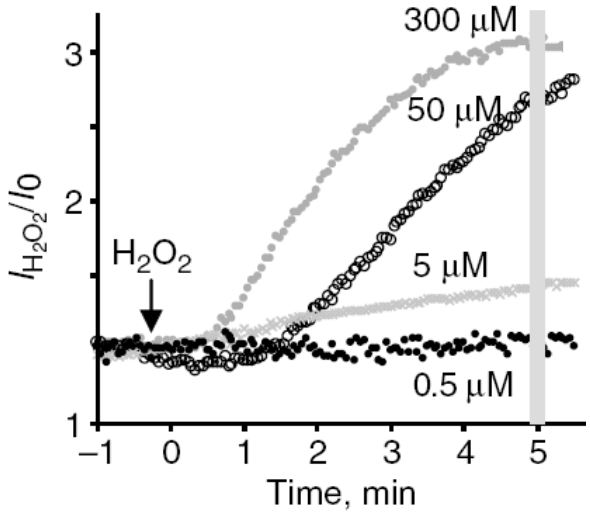
SP induces ROS release in DRG

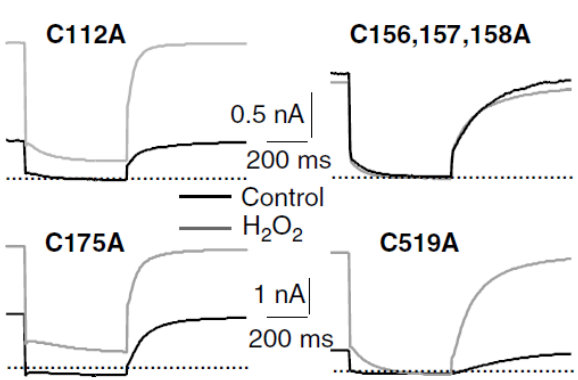


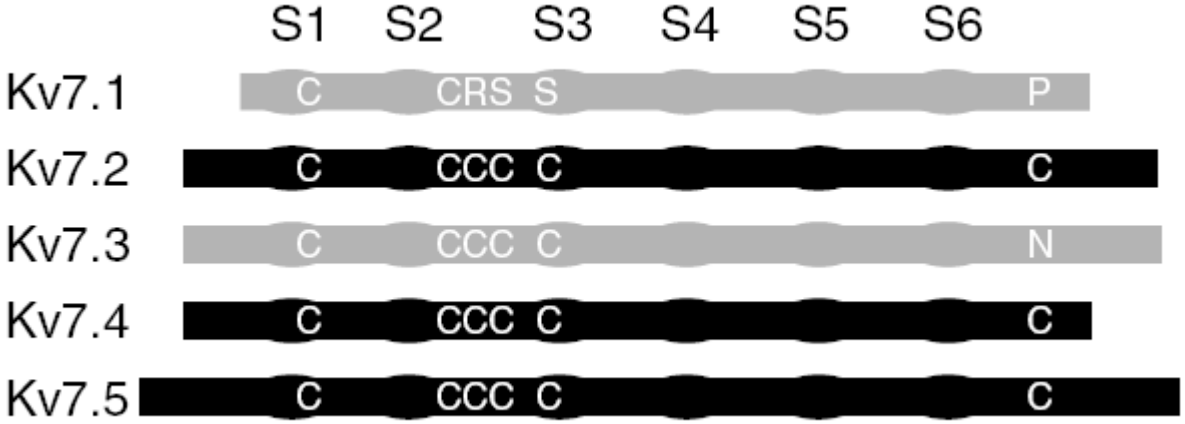
Linley et al PNAS 2012

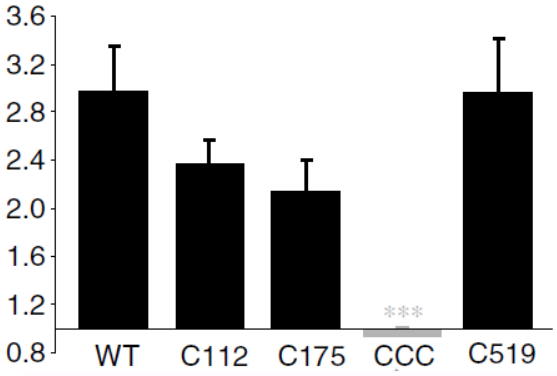
M-type (Kv7, KCNQ) channels are potentiated via oxidative modification



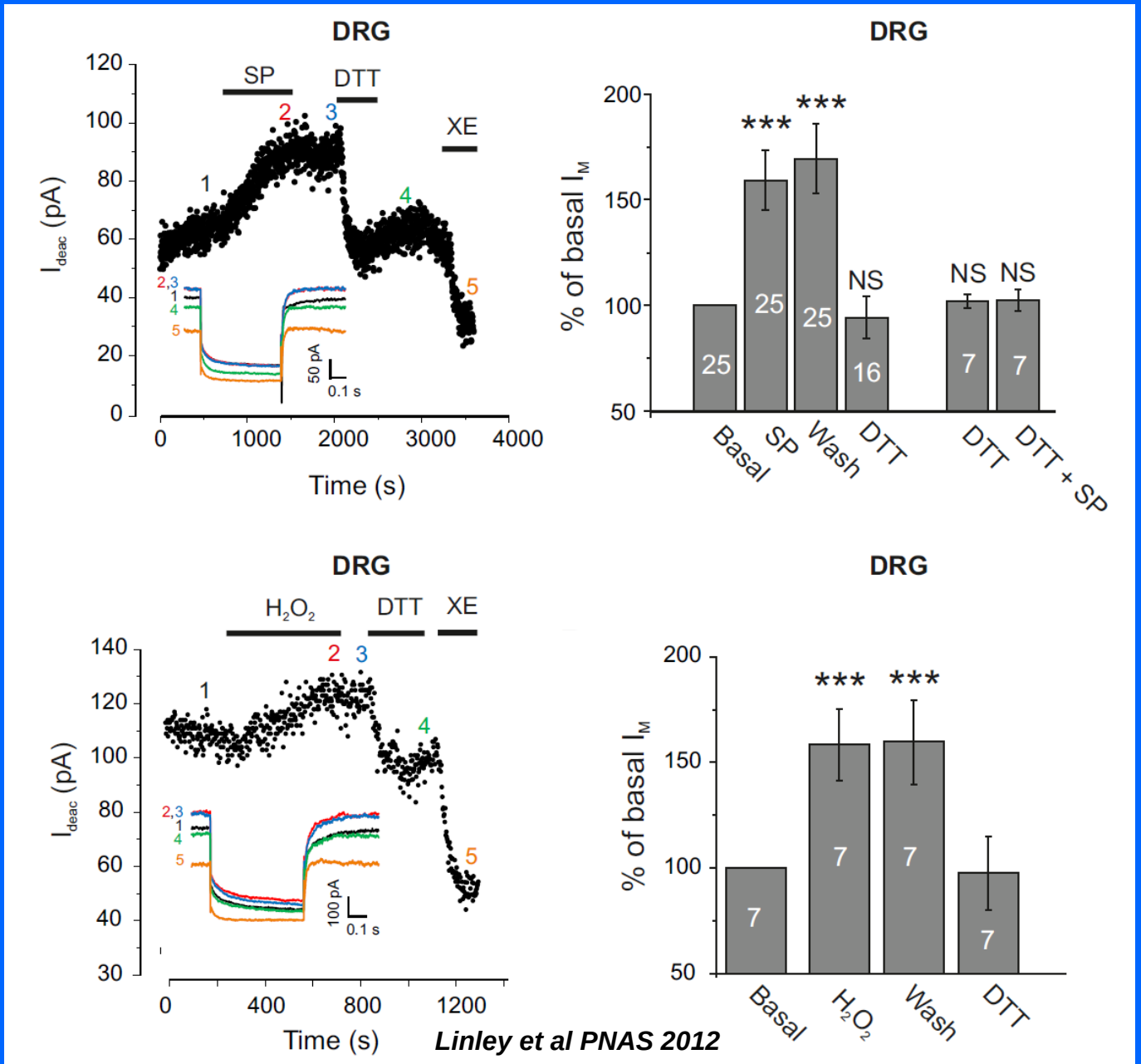






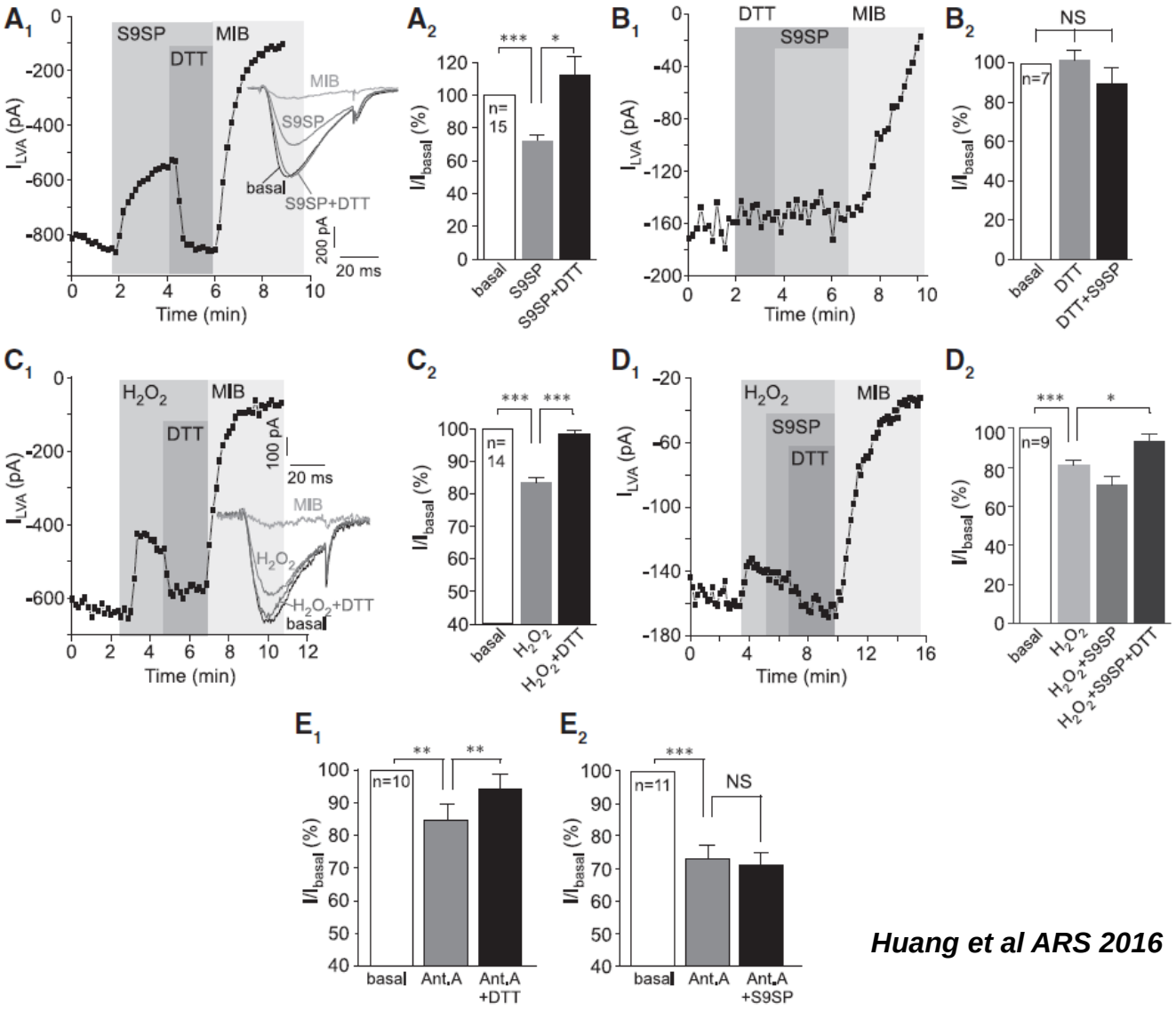


SP augments M current in DRG neurons in a redox-dependent manner



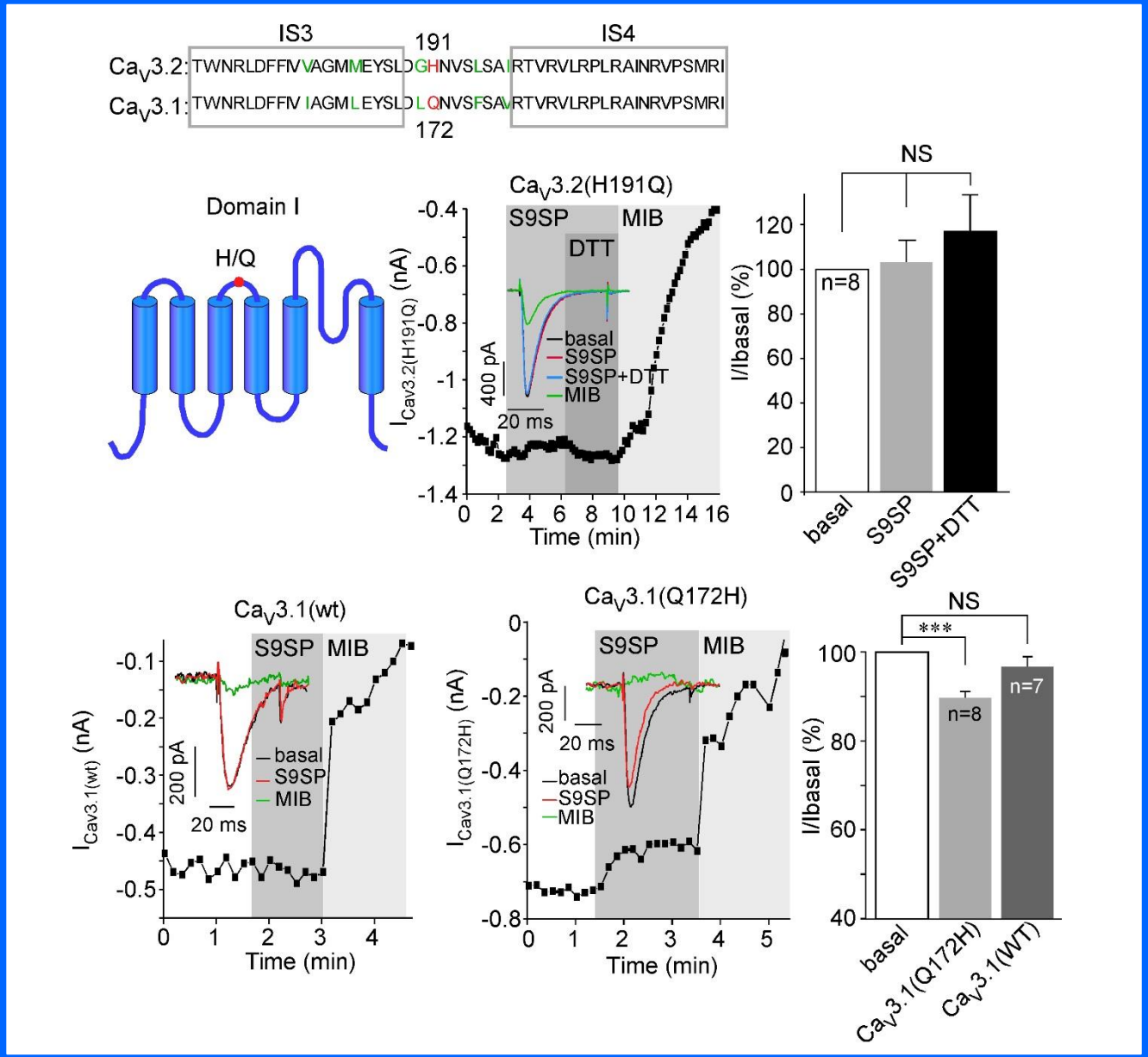
Linley et al PNAS 2012

SP also inhibits T-type Ca^{2+} channels which are also redox-sensitive



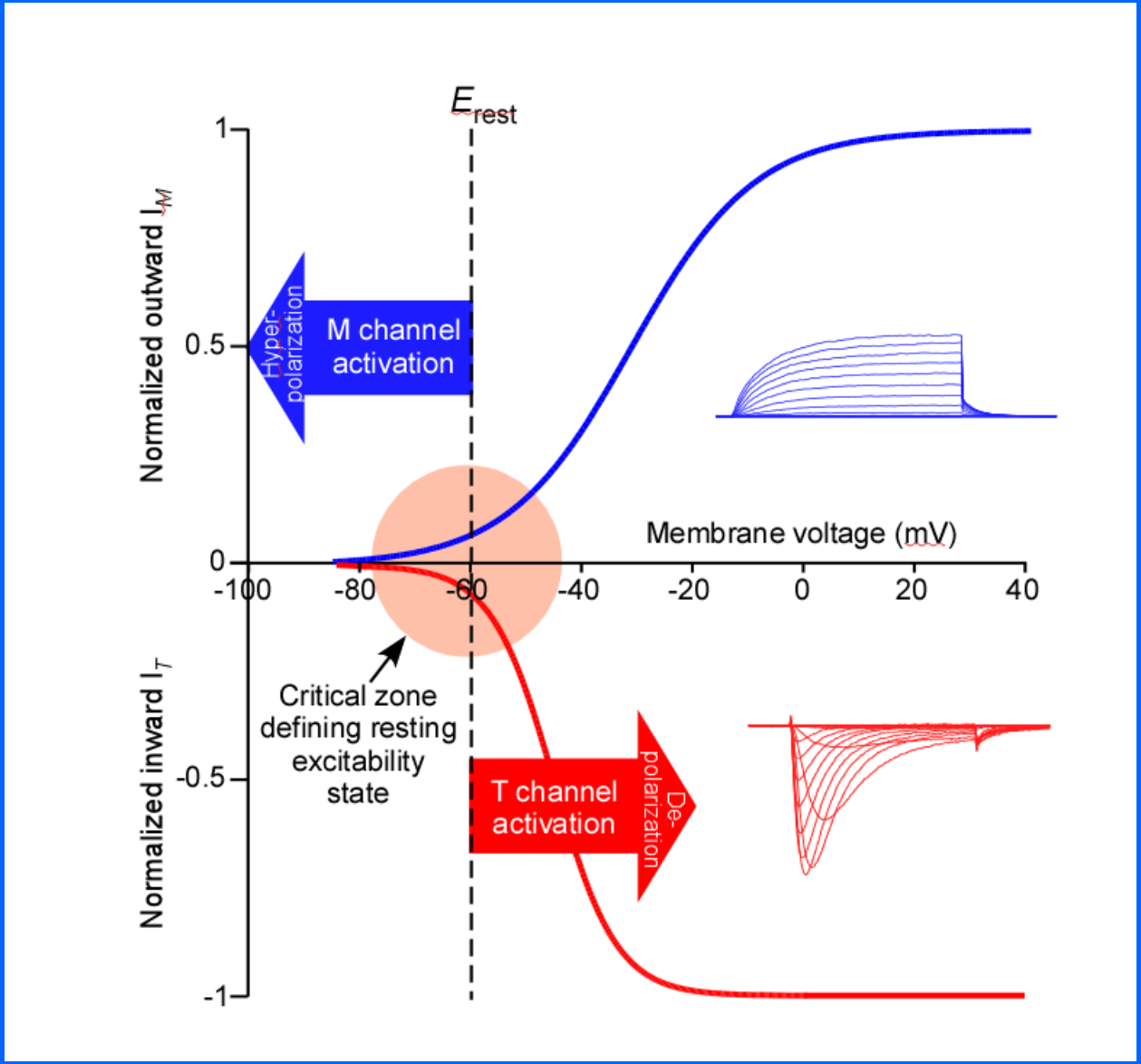
Huang et al ARS 2016

Redox/zinc-sensitive site within Cav3.2 makes this subunit sensitive to modulation by SP

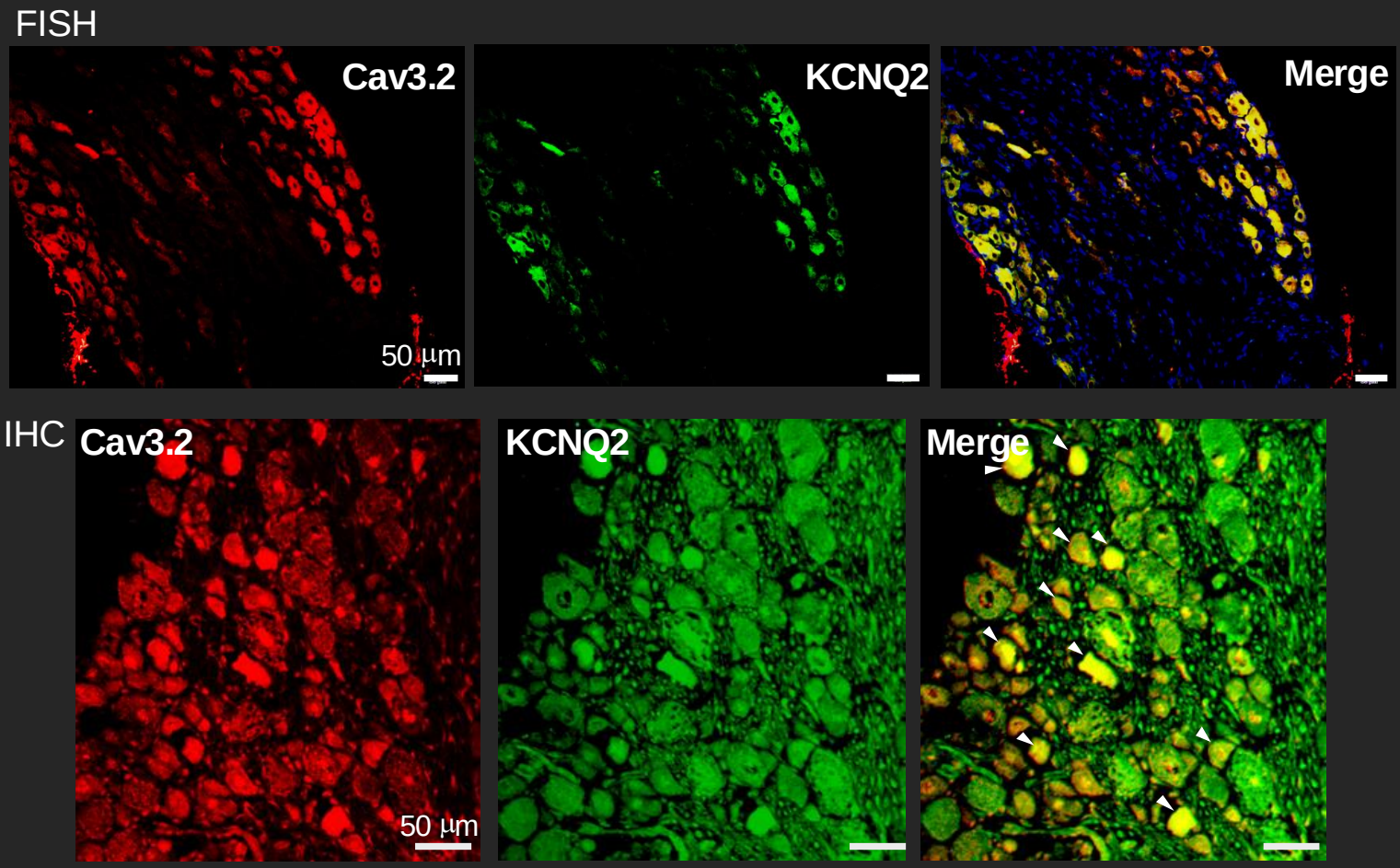


Huang et al ARS 2016

M- and T-type channels contribute to resting excitability setting

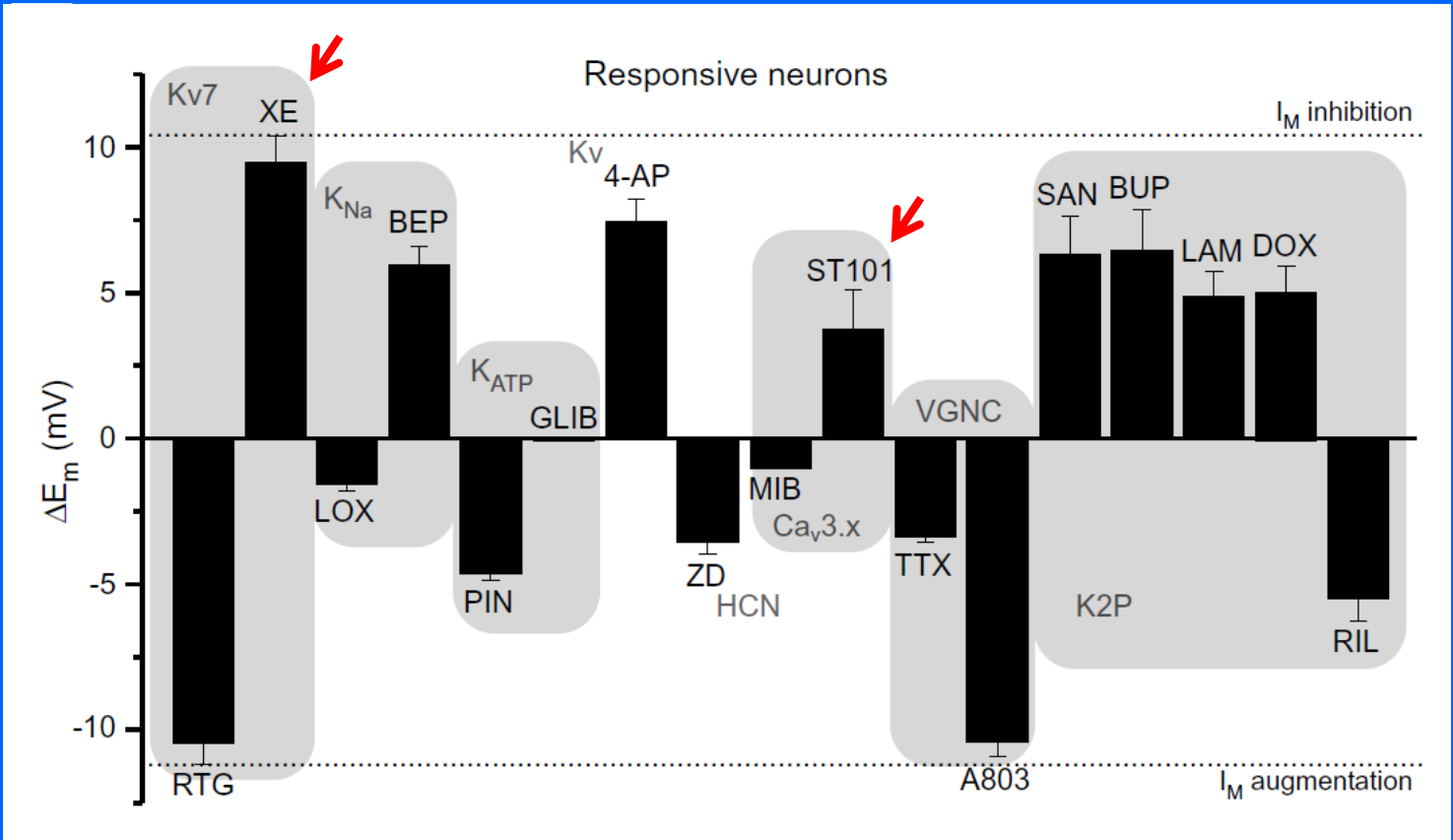


M- and T-type channels are coexpressed in many small-diameter FRG neurons



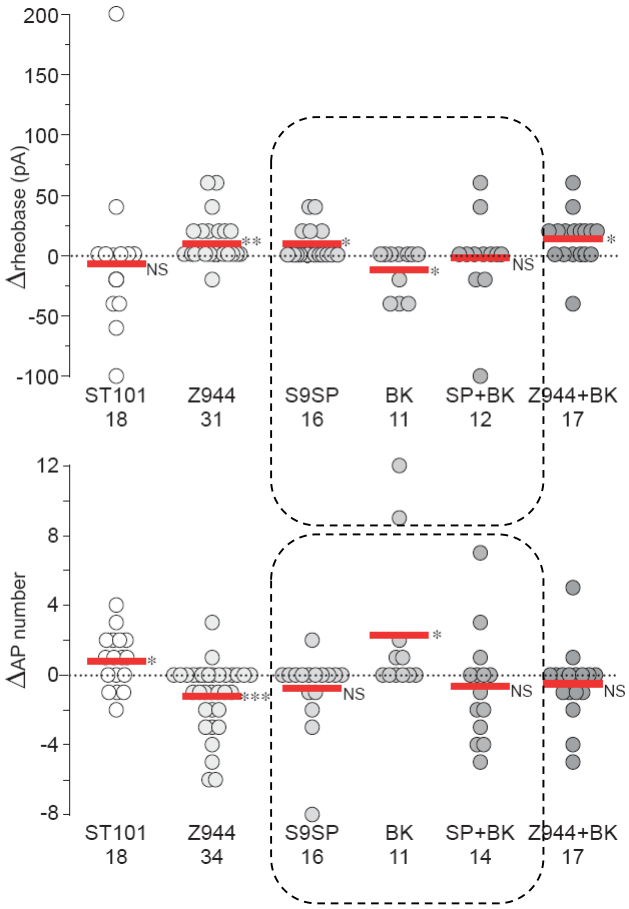
Huang et al ARS 2016

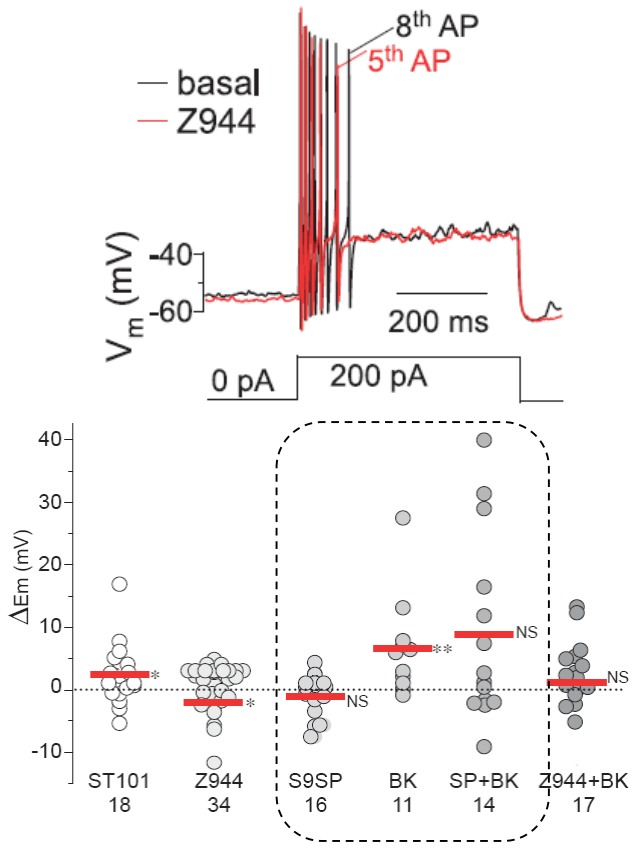
Both M- and T-type channel activity influences resting membrane potential of DRG neurons



Du et al Pain 2014

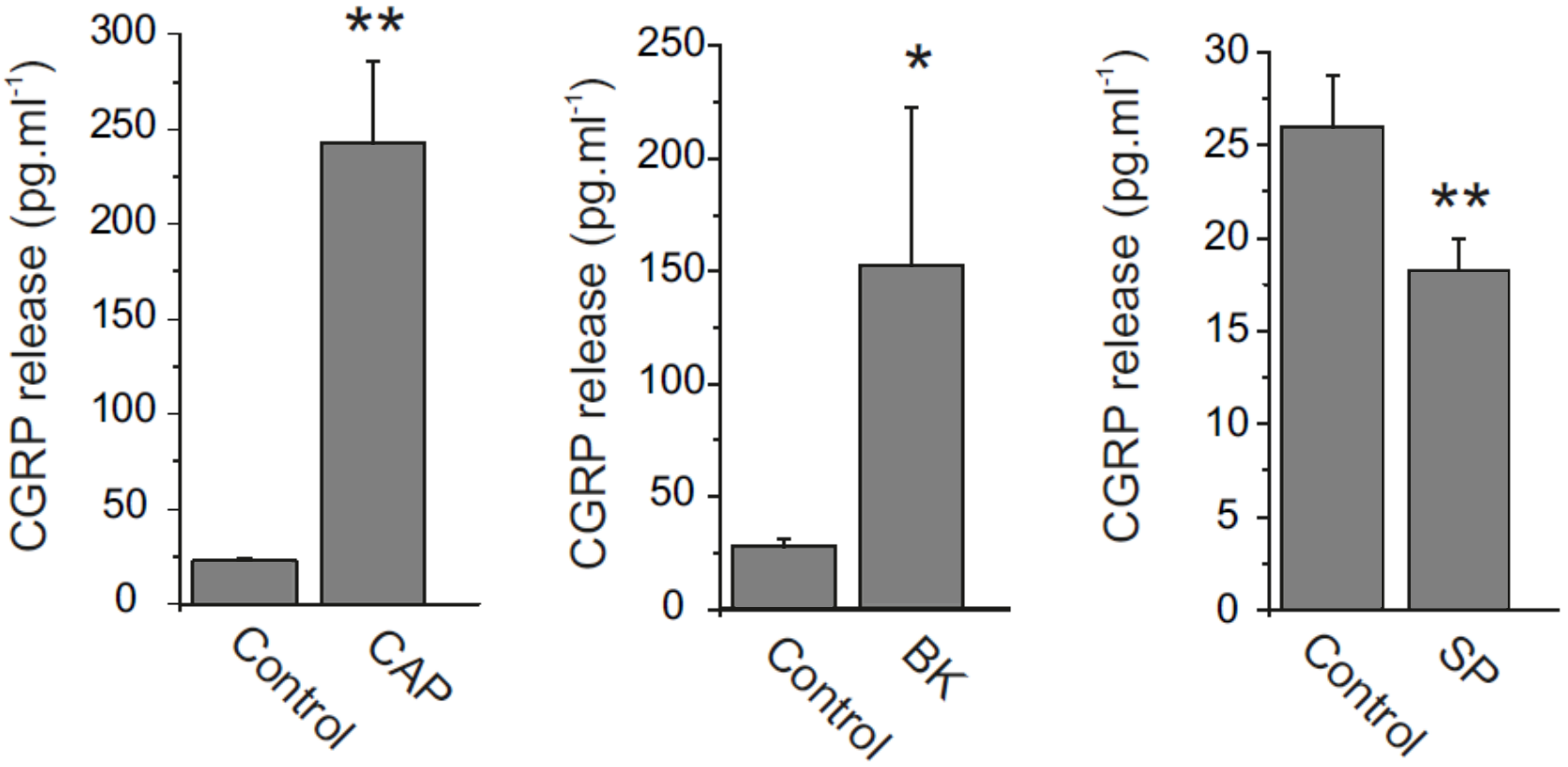
SP produces anti-excitatory effects in DRG





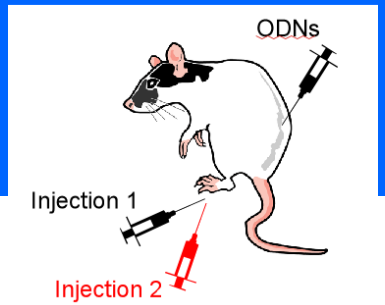
Huang et al ARS 2016

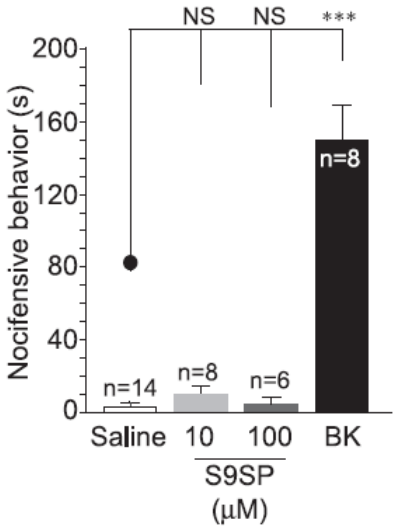
BK expectedly induces release of CGRP by DRG, but SP not only does not induce CGRP release but reduces the basal release

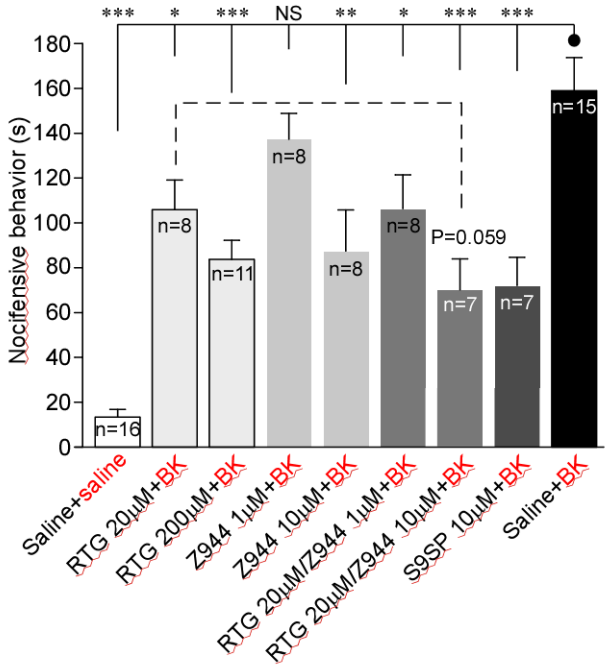


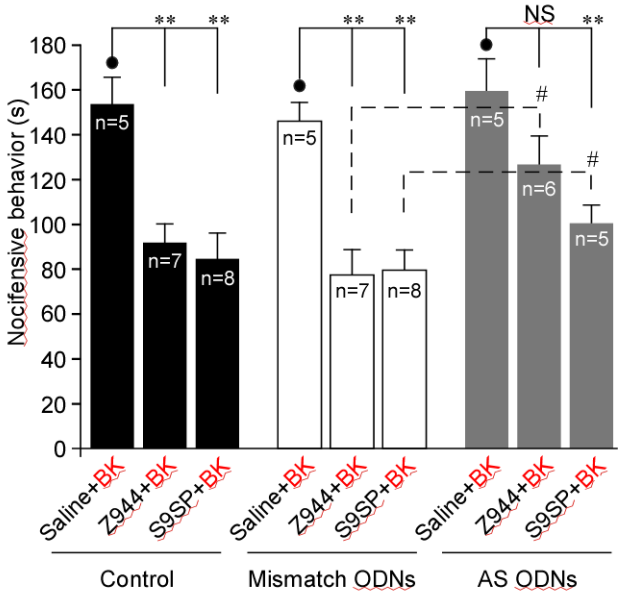
Linley et al PNAS 2012

Peripheral injections of SP produce no pain but reduces BK-induced pain

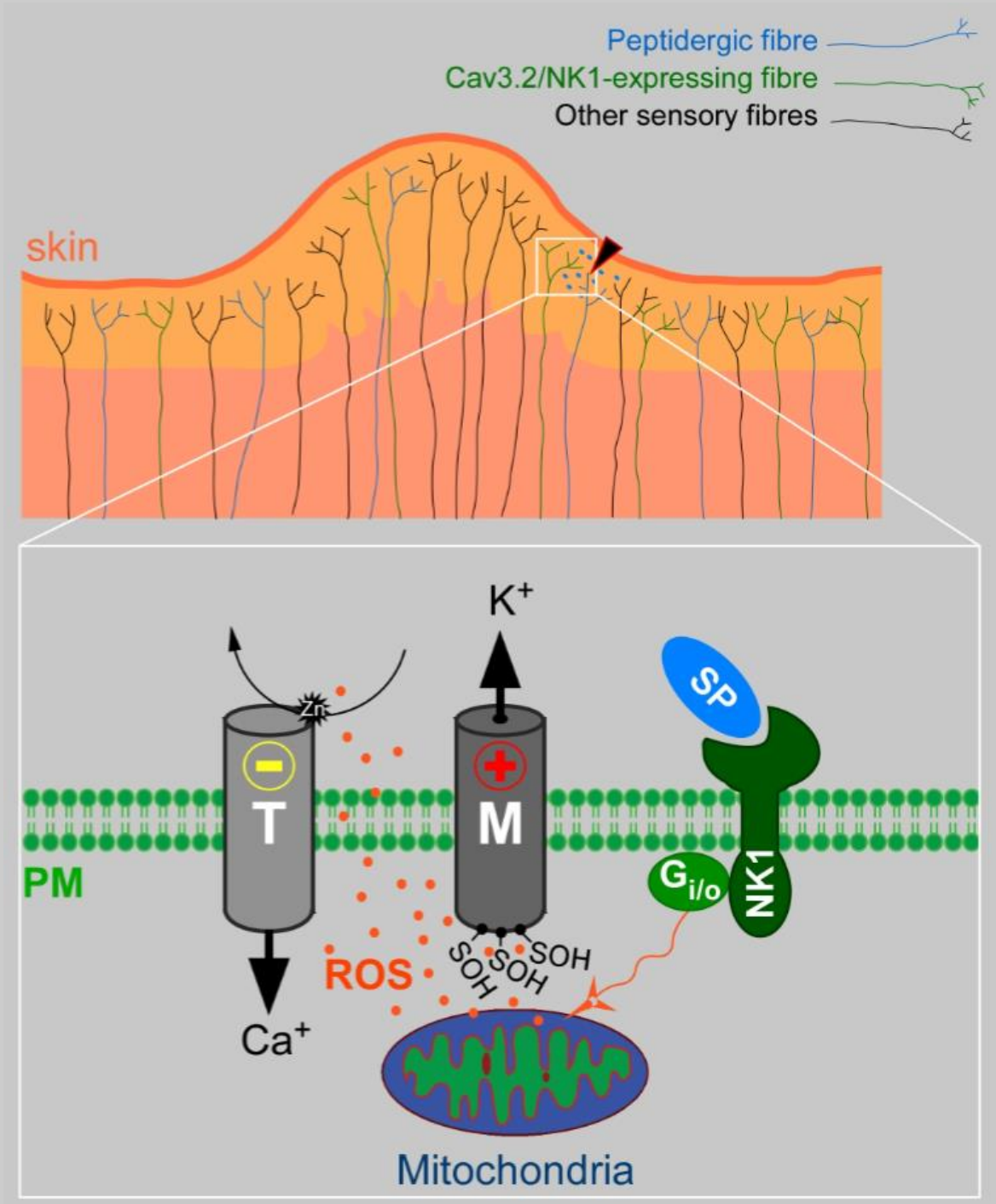








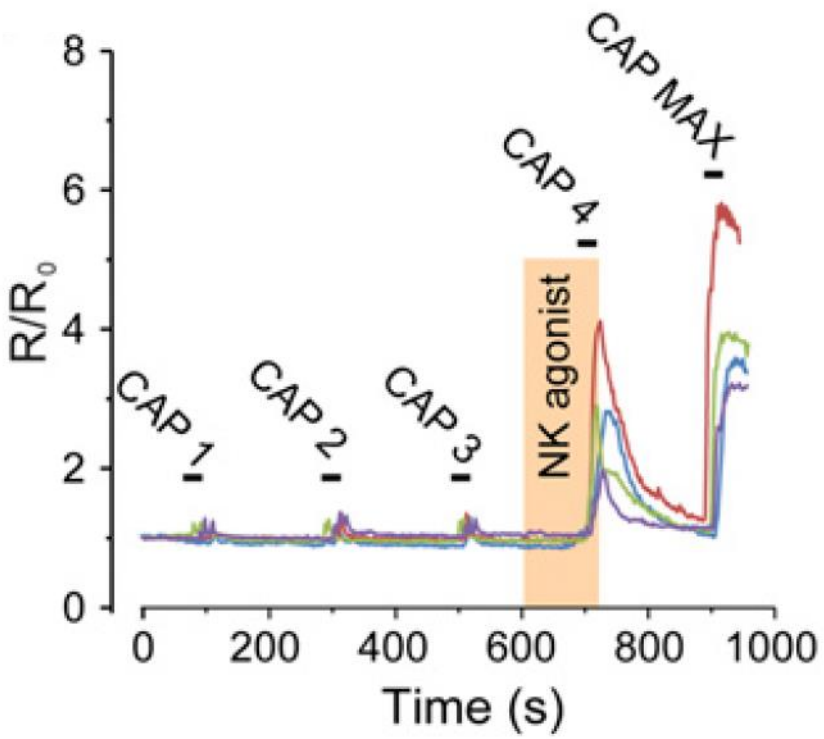
Huang et al ARS 2016



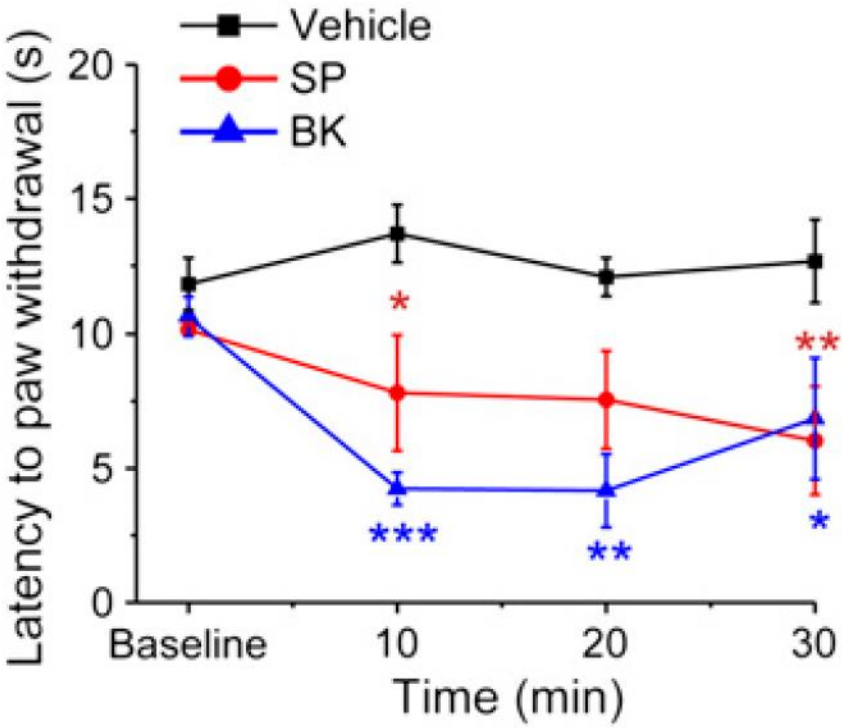
Huang et al ARS 2016

SP does produces slight thermal hyperalgesia though

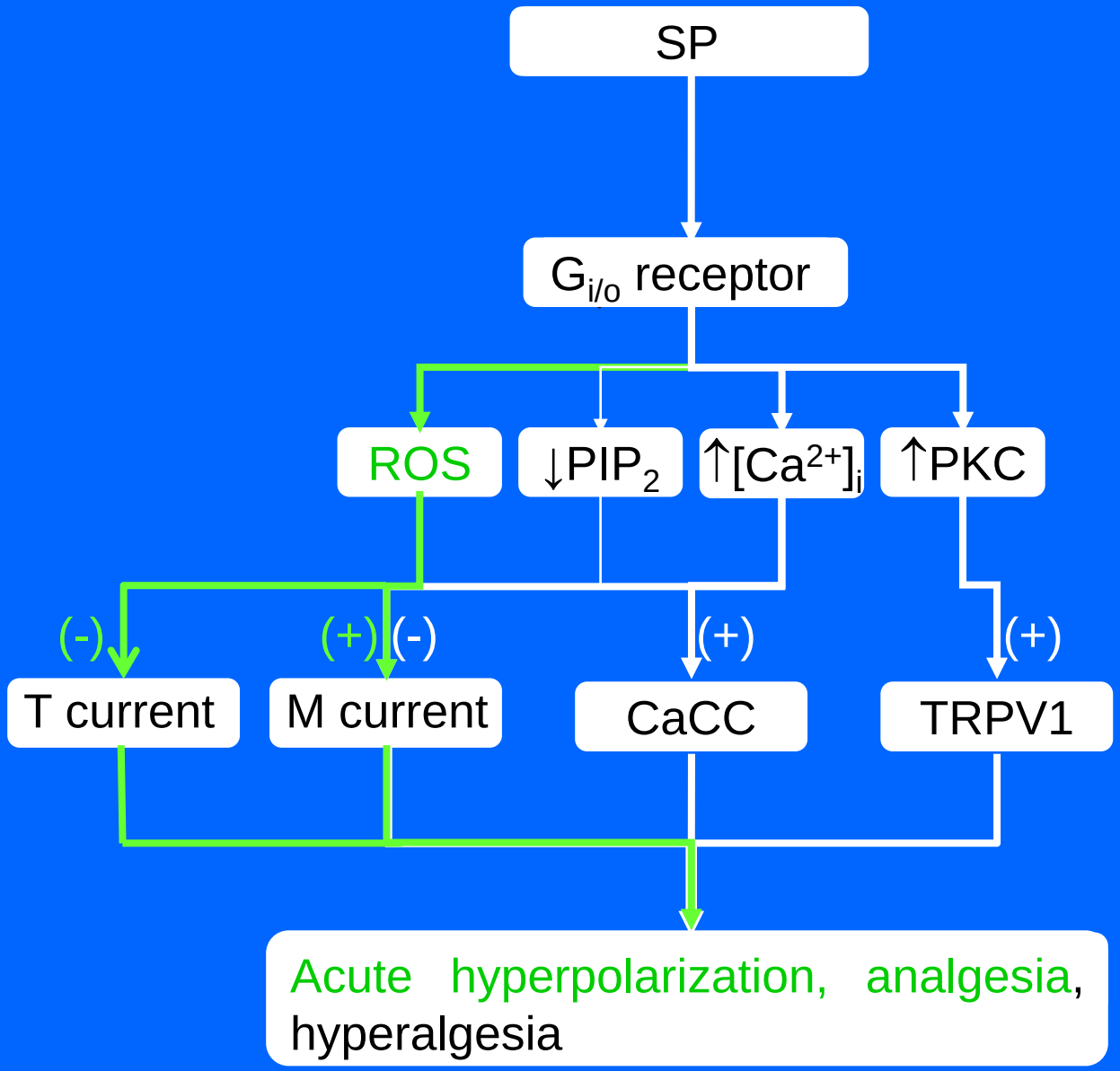
Ca^{2+} imaging



Hargreaves test



Linley et al PNAS 2012


SP
$G_{i/o}$ receptor
ROS
$\downarrow PIP_2$
$\uparrow [Ca^{2+}]_i$
$\uparrow$PKC
(-)
(+)
(-)
(+)
(+)
T current
M current
CaCC
TRPV1
Acute hyperpolarization, analgesia, hyperalgesia

Gamper's lab (Leeds)

Hebei Medical University, China

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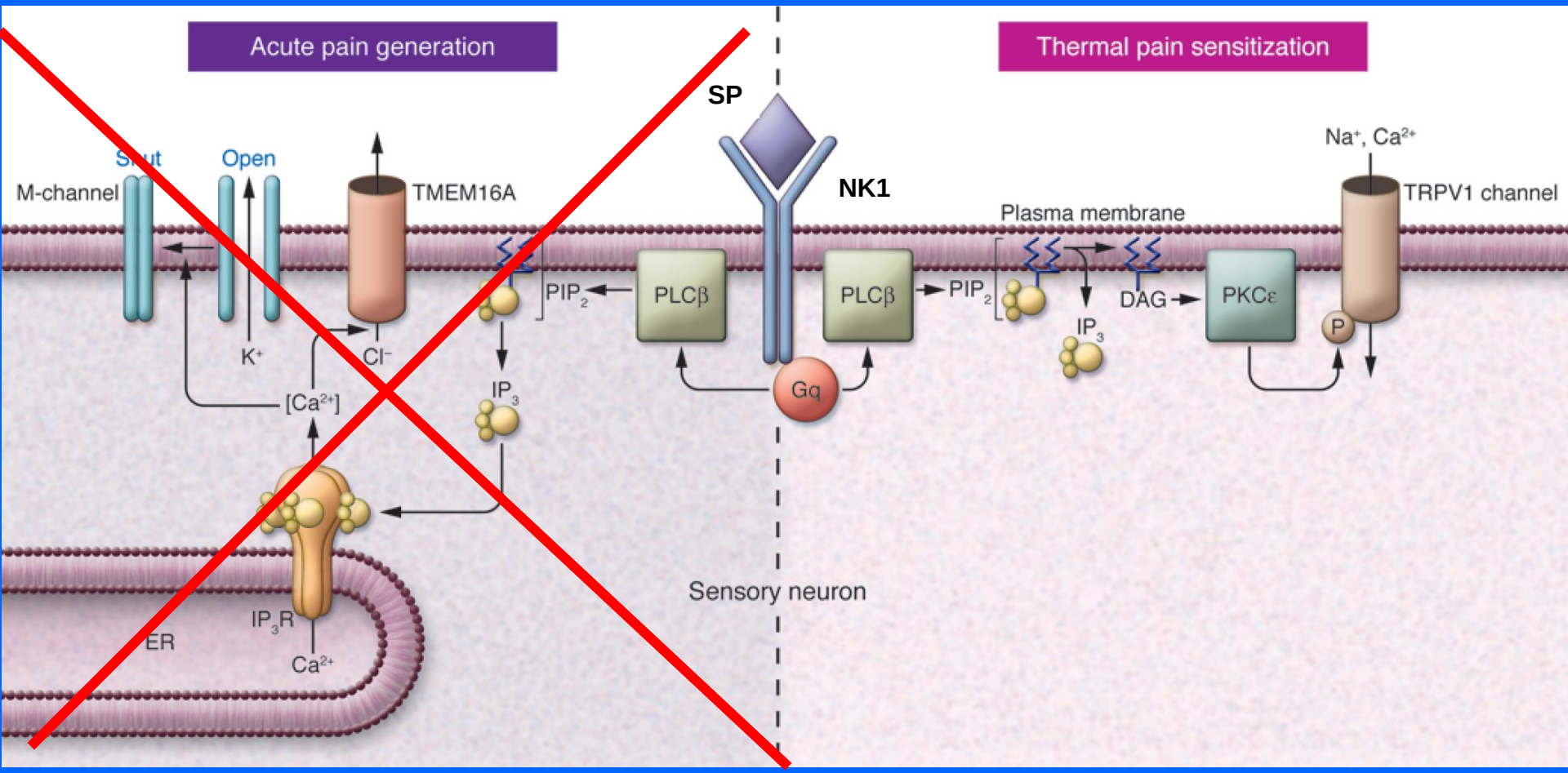
Lezanne Ooi
Haixia Gao
Kirsty Rose
Louisa Pettinger
Shihab Shah
Xin Jin
Hannah Kirton
Katarzyna Marszalek
Ewa Jaworska
Aurelian Bolliat
Alexandra Gerghina

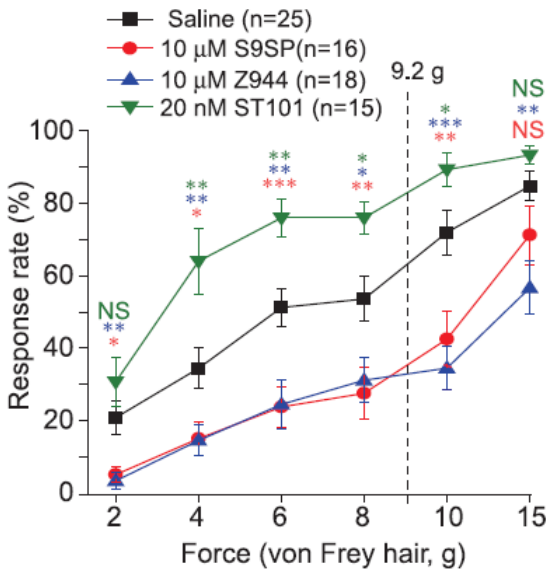
Hailin Zhang

Xiaona Du
Dongyang Huang
Han Hao
Boyi Liu
Fan Zhang
Liu Yani
Huiran Zhang
Zhanfeng Jia

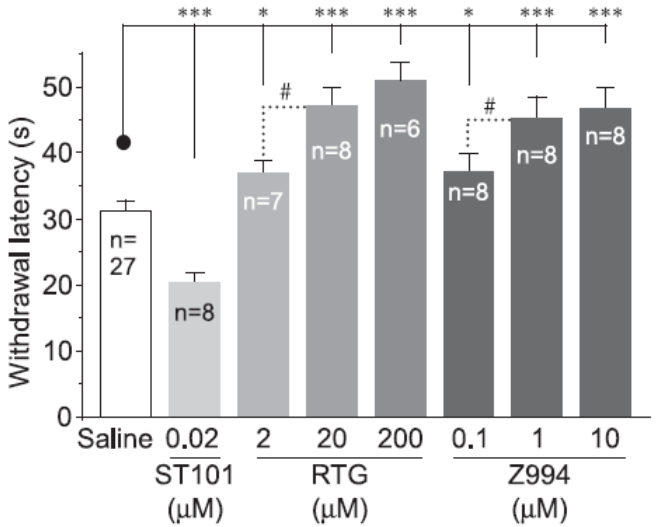

Acute pain generation
Thermal pain sensitization
SP
NK1
Shut
Open
M-channel
TMEM16A
K+
Cl−
[Ca2+]
PIP2
PLCβ
IP3
Gq
Plasma membrane
DAG
PKCε
P
Na+, Ca2+
TRPV1 channel
IP3R
ER
Ca2+
Sensory neuron

Peripheral injections of SP produce no pain but reduces basal sensitivity to mechanical and thermal stimulation

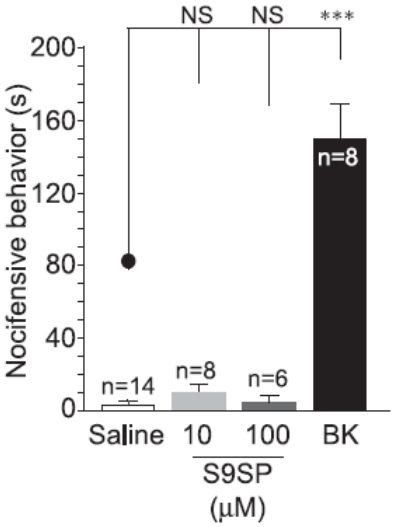
Mechanical sensitivity



Thermal sensitivity

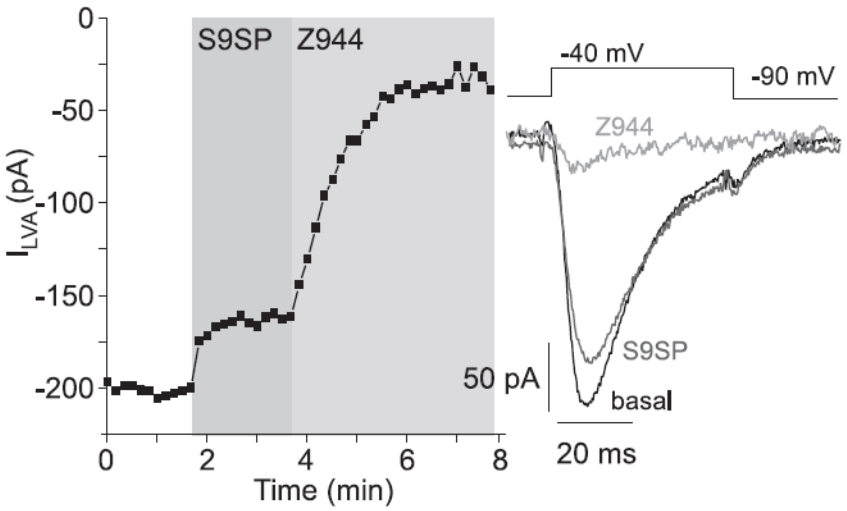


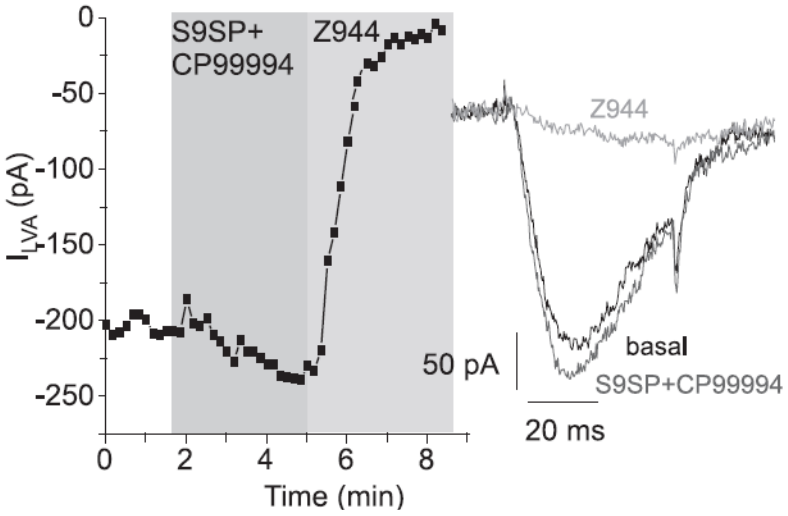
Persistent pain

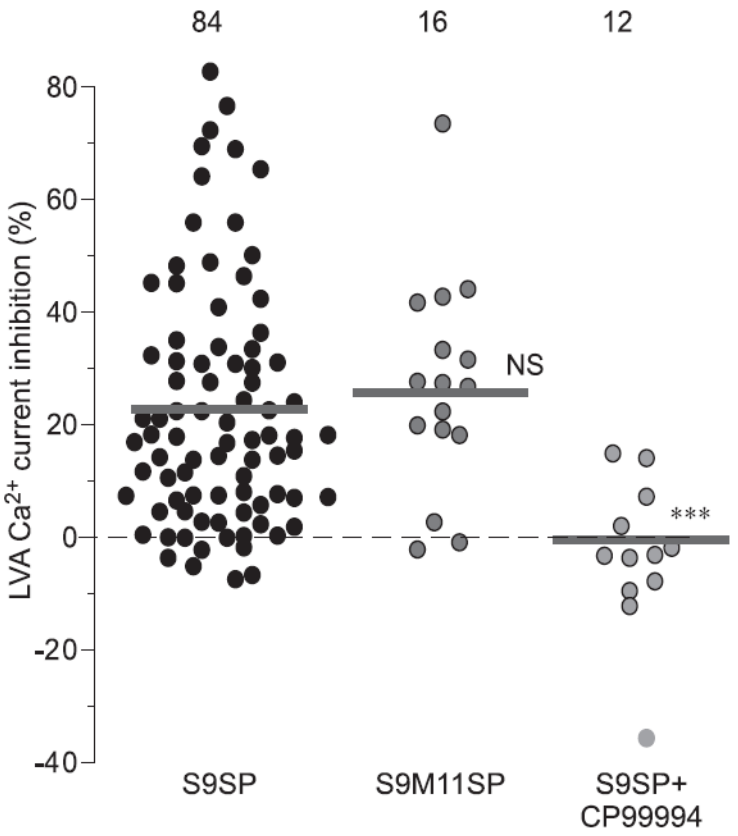


Huang et al ARS 2016

There is another redox-sensitive current in DRG… T-type Ca^{2+} current and it is also affected by SP







Huang et al ARS 2016