Nociceptors – *characteristics?*

- ?
- ?
- ?
- ?
- ?
- ?

Nociceptors - true/false

- Nociceptors
- All C fibers are nociceptors
- Nociceptors have small diameter somata
- All nociceptors express TRPV1 channels
- Nociceptors have high thresholds for response
- Nociceptors have only afferent (sensory) functions
- Nociceptors encode stimuli into the noxious range

Typically yes, but there is a semantic problem

activation

tissue

Nociceptors – *outline*

Why are nociceptors important?

What's a nociceptor?

Nociceptor properties – somata, axons, content, etc.

Nociceptors in skin, muscle, joints & viscera

Mechanically-insensitive nociceptors (sleeping or silent)

Microneurography

Heterogeneity

Why are nociceptors important?

- Pain relief when remove afferent drive
- Afferent is more accessible
- With peripherally restricted intervention,

IASP

PAIN® 155 (2014) 1272–1279

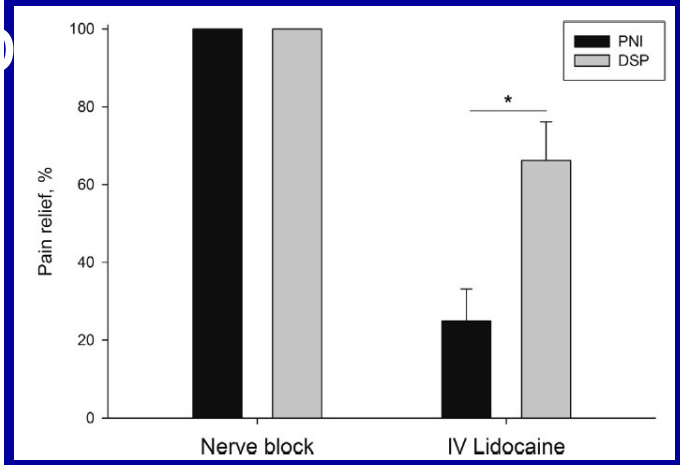
PAIN®

www.elsevier.com/locate/pain

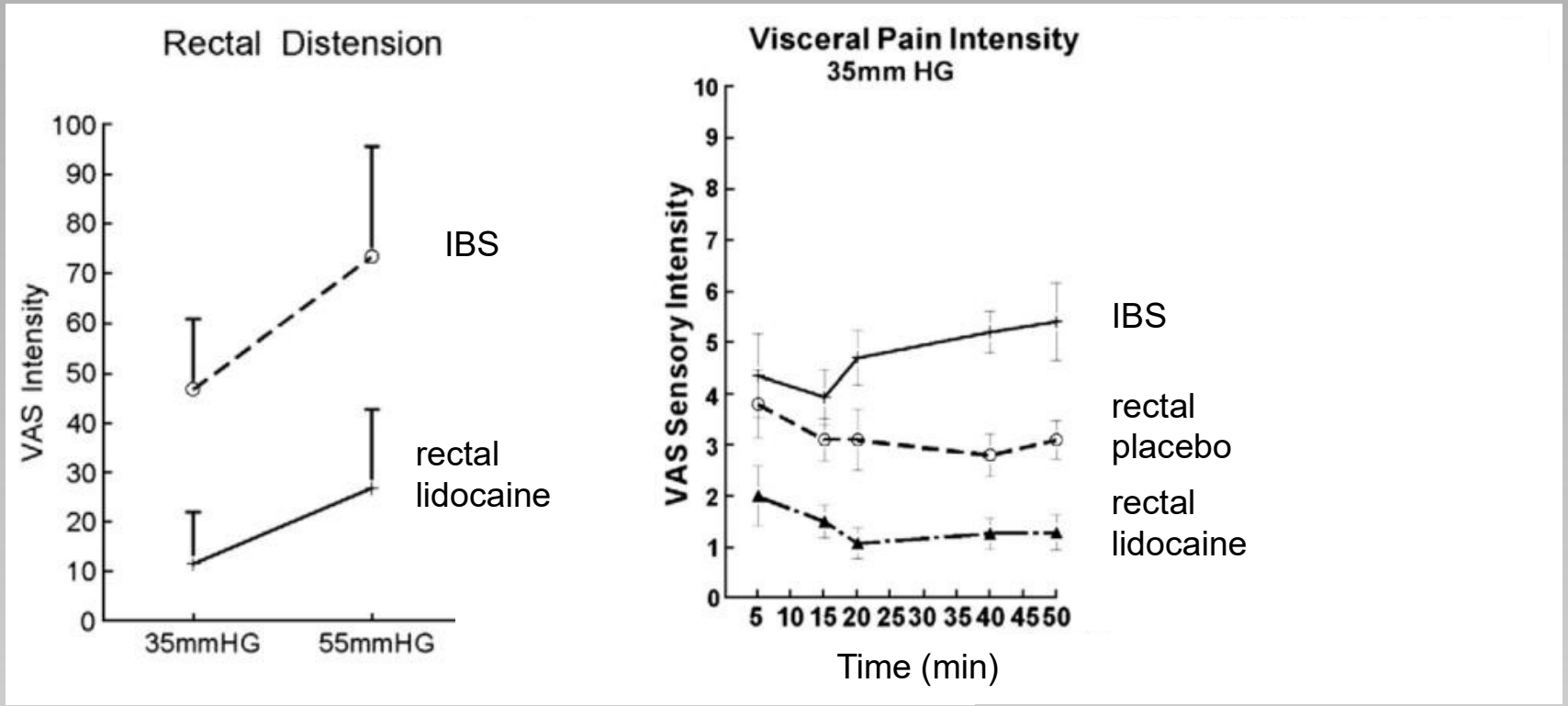
Primary afferent input critical for maintaining spontaneous pain in peripheral neuropathy

Simon Haroutounian [a,*], Lone Nikolajsen [a,b], Thomas F. Bendtsen [b], Nanna B. Finnerup [a], Anders D. Kristensen [b], Jørgen B. Hasselstrøm [c], Troels S. Jensen [a,d]

[a] Danish Pain Research Center, Aarhus University Hospital, Aarhus, Denmark
[b] Department of Anesthesiology, Aarhus University Hospital, Aarhus, Denmark
[c] Section for Toxicology and Drug Analysis, Department of Forensic Medicine, Aarhus University, Aarhus, Denmark
[d] Department of Neurology, Aarhus University Hospital, Aarhus, Denmark



Widespread hyperalgesia in irritable bowel syndrome is dynamically maintained by tonic visceral impulse input ….
Price DD, Craggs JG, Zhou Q, Verne GN, *et al*.
Neuroimage 47:995-1001, 2009



Importantly, areas of somatic referral were also significantly reduced in size.

What's a nociceptor ?

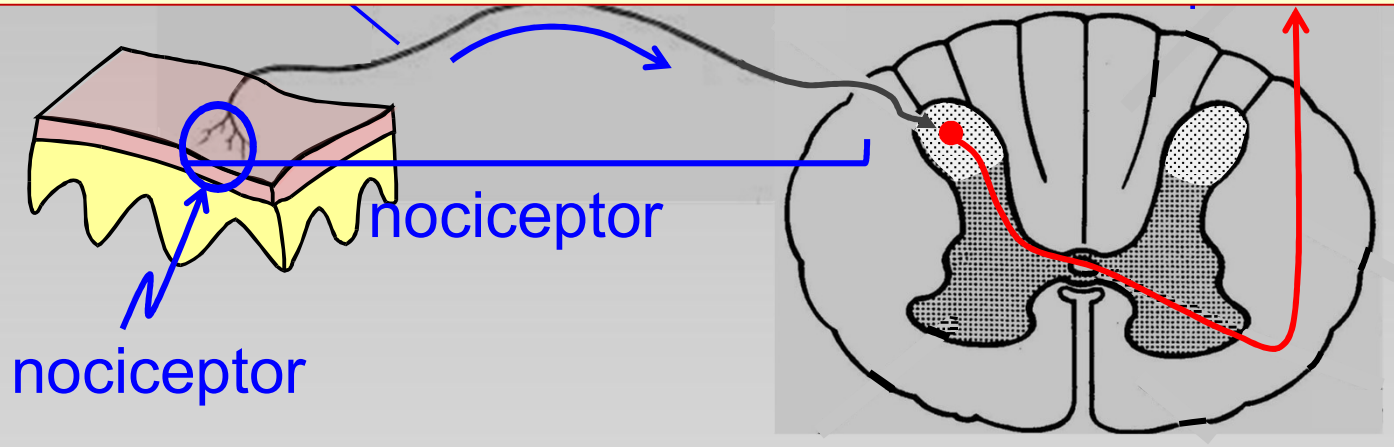
……. first, recall these definitions

Pain - Nociception

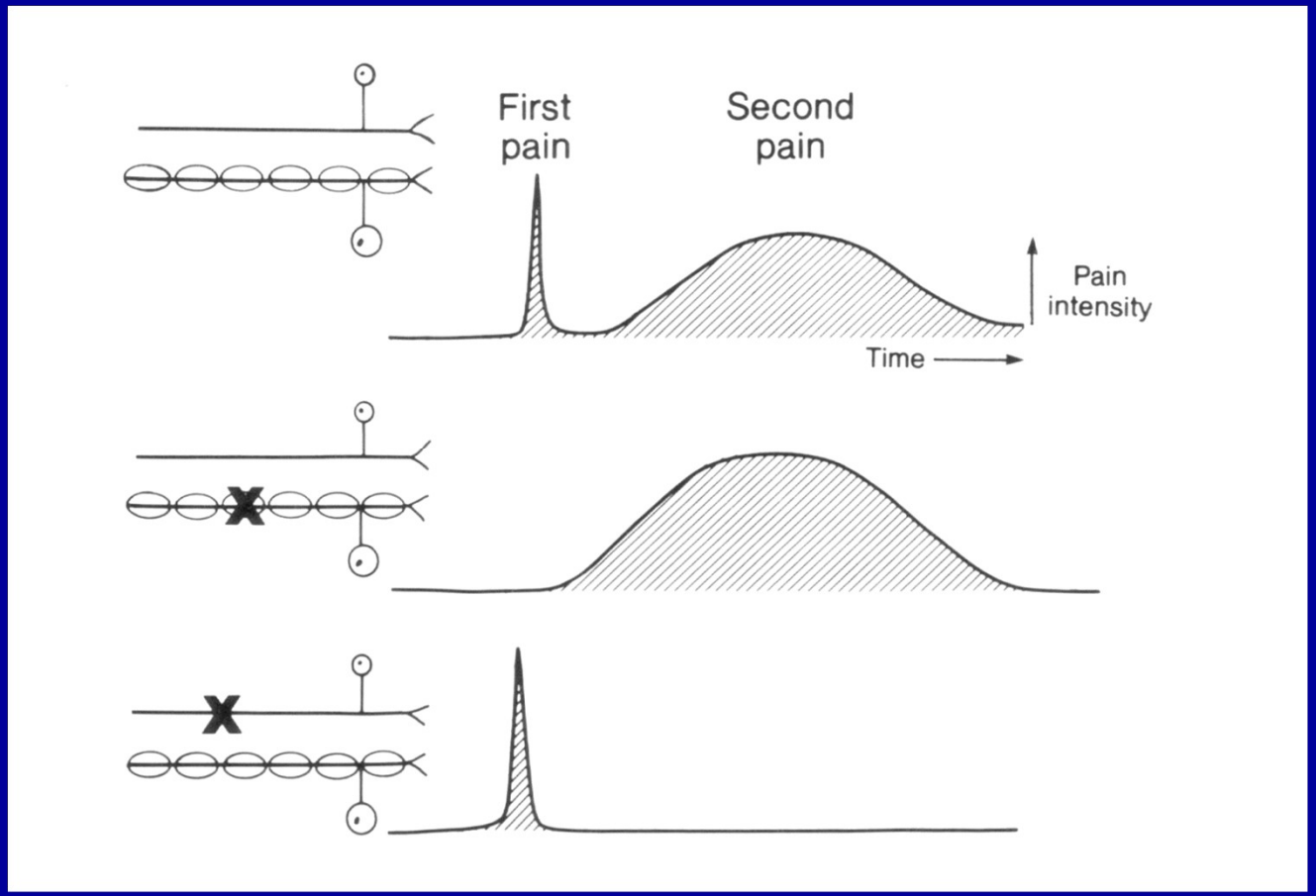
- *Pain:* an unpleasant sensory *and* emotional experience associated with actual or potential tissue damage; pain is always subjective
- *Nociception:* introduced by Sherrington to make clear the distinction between detection of a noxious event and the psychological and other responses to it (including 'pseudaffective' responses)

What's a Nociceptor ? - Sherrington

- Stimuli *adequate* to activate nociceptors are
- different in different tissues:
  - **skin** – cutting, crushing, burning
  - **viscera** – traction on the mesentery, hollow organ stretch/distension
  - **muscle, joints, bone** – 'chemical'

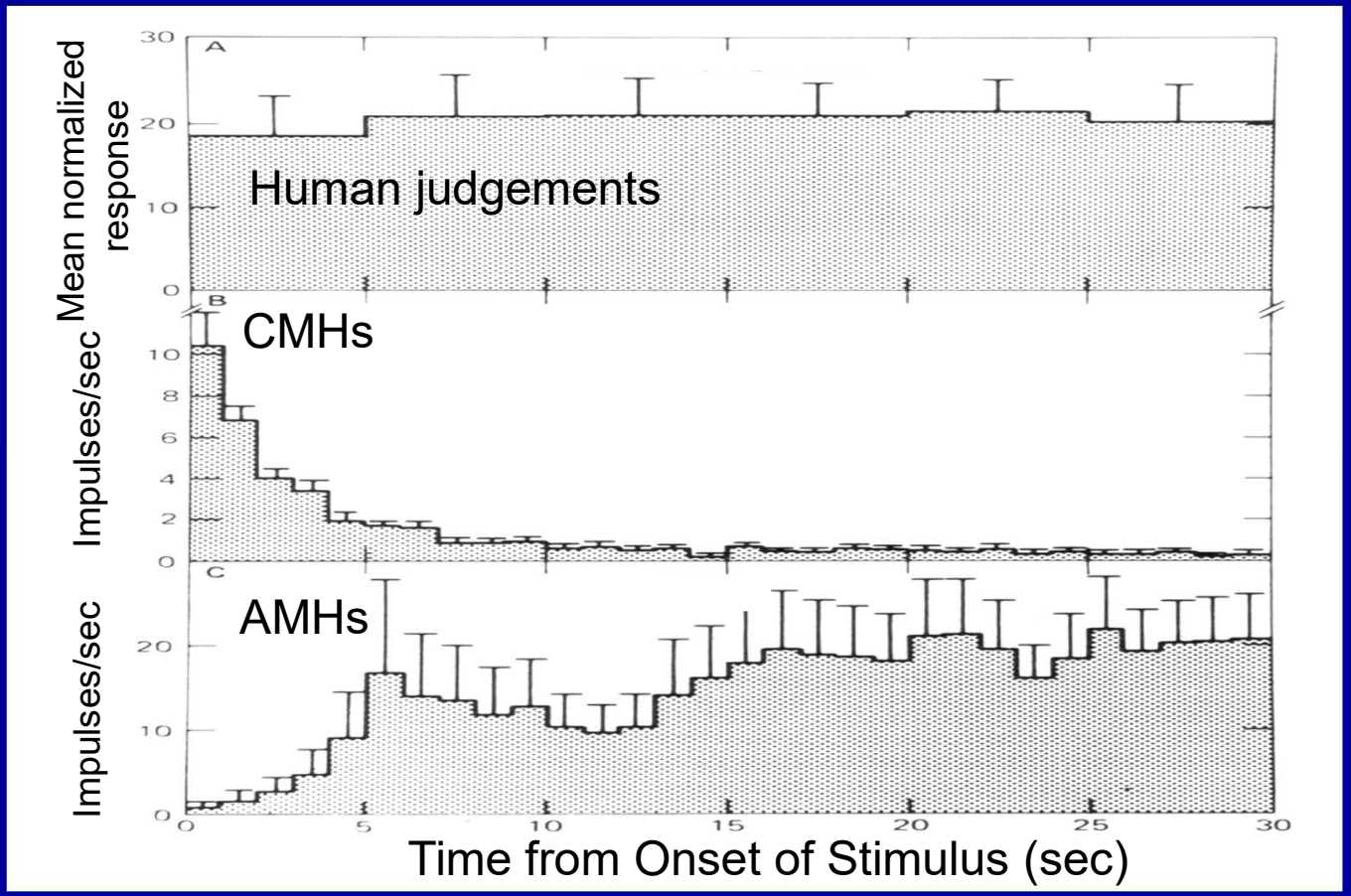


Subpopulation Specificity



Fields, H.L., Pain 1987

Functional Implications



Meyer et. al., Textbook of Pain, Wall and Melzack Eds., Churchill Livingstone, 1994

Nociceptor Classification: **Modalities of Stimuli**

» Transducer: apparatus that converts one form of energy to another

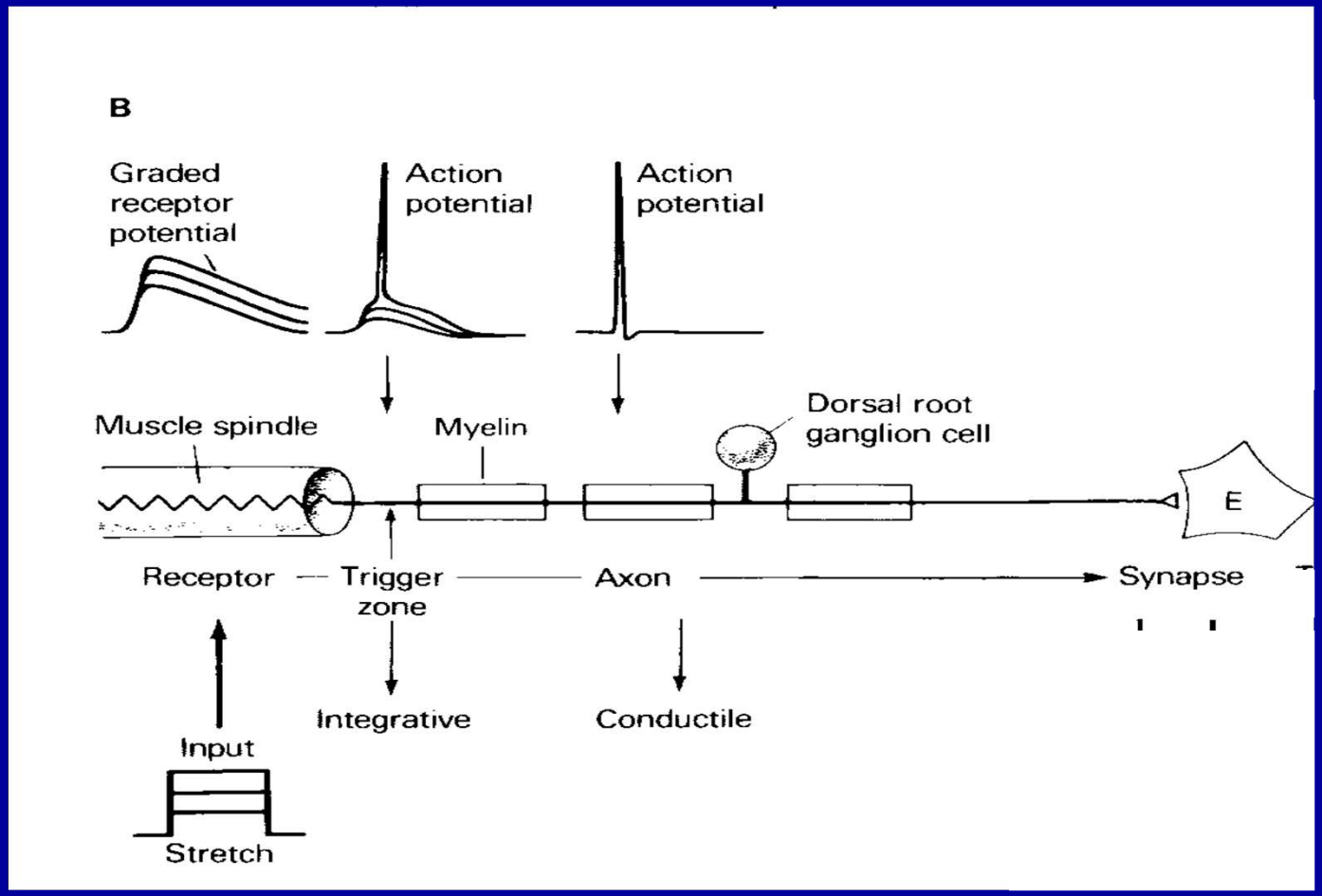
– Thermoreceptors

– Mechanoreceptors

– Chemoreceptors

– “Silent”, “Mechanically Insensitive”

Stimulus Transduction

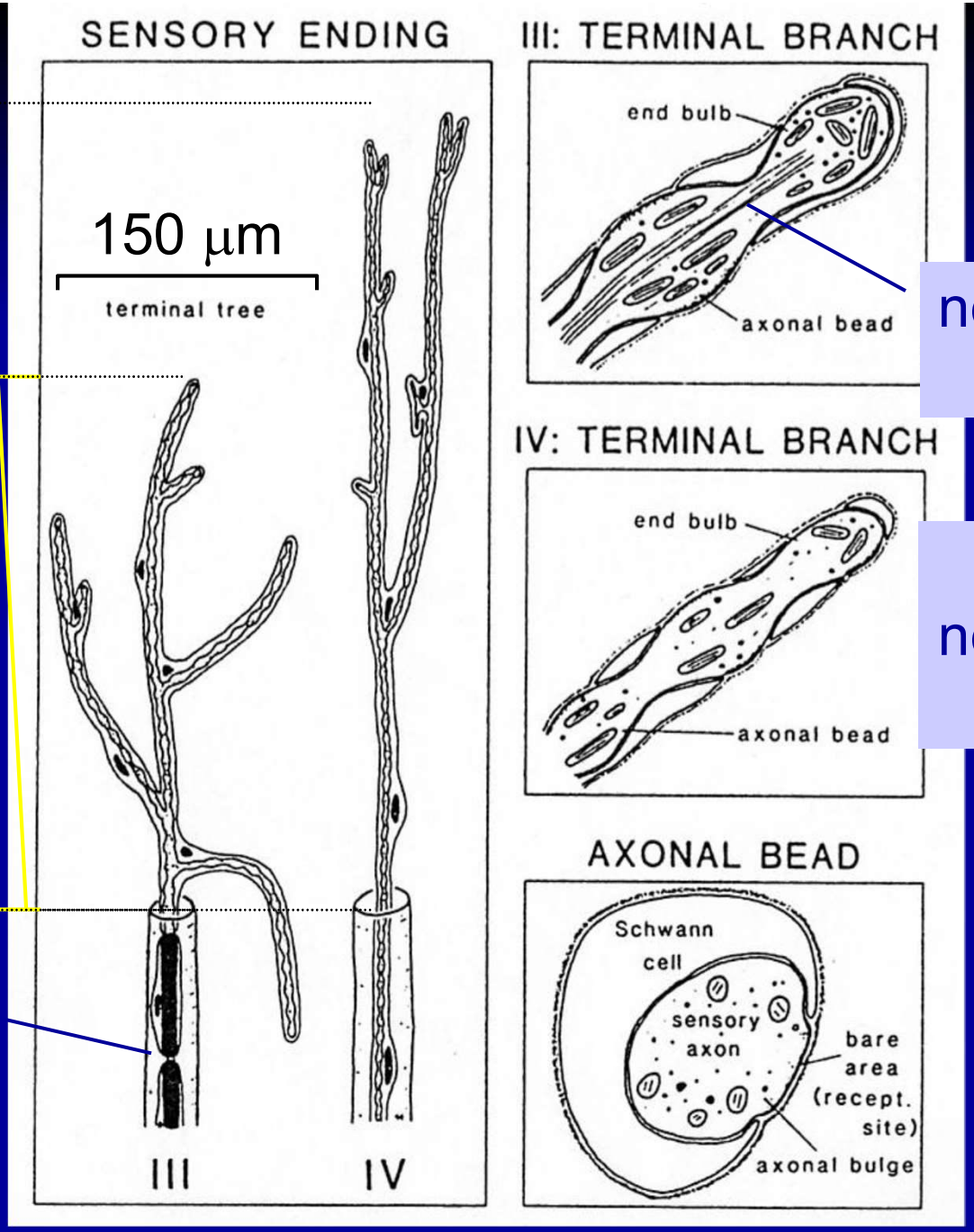


Kandel and Schwartz Principles of Neuroscience, Elsevier 1985

≤300 μm length
fiber diameter:
0.3 – 0.55 μm

≤200 μm length
fiber diameter:
1.0 –1.5 μm

perineurium
(a blood –nerve
barrier)



neurofilament
core

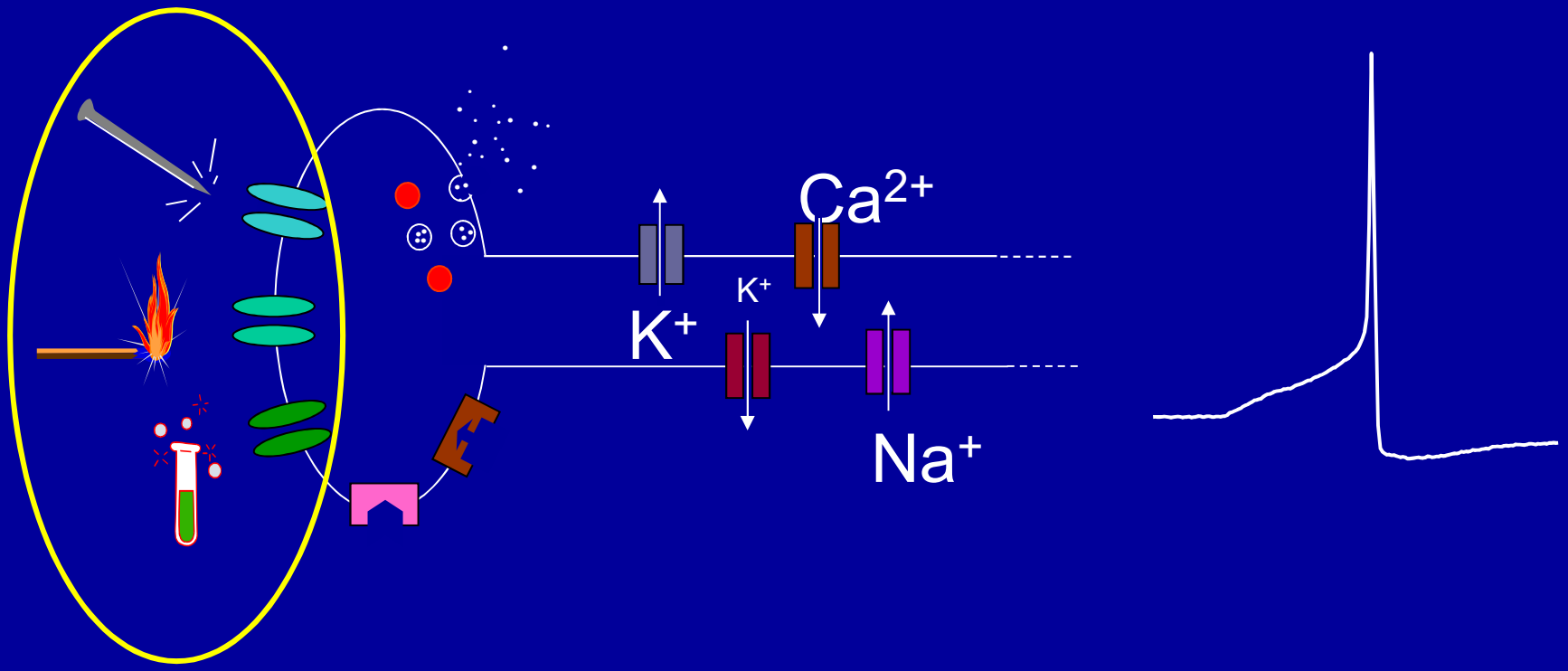
no
neurofilament
core

Schmidt and Messlinger, 1994

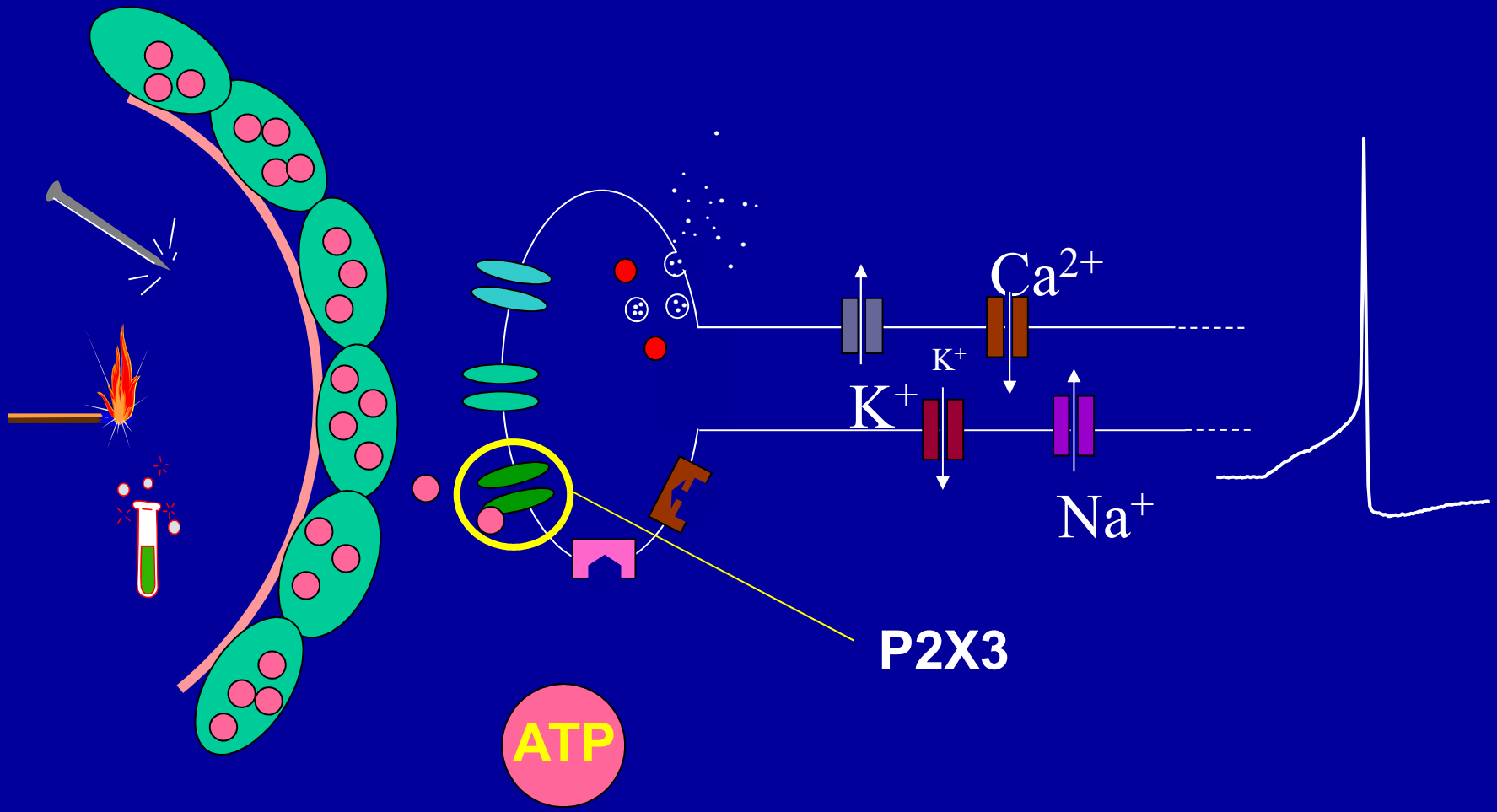
“Direct” Transduction

Transmitter Release

Transduction Spike Initiation Propagation



“Indirect” Transduction

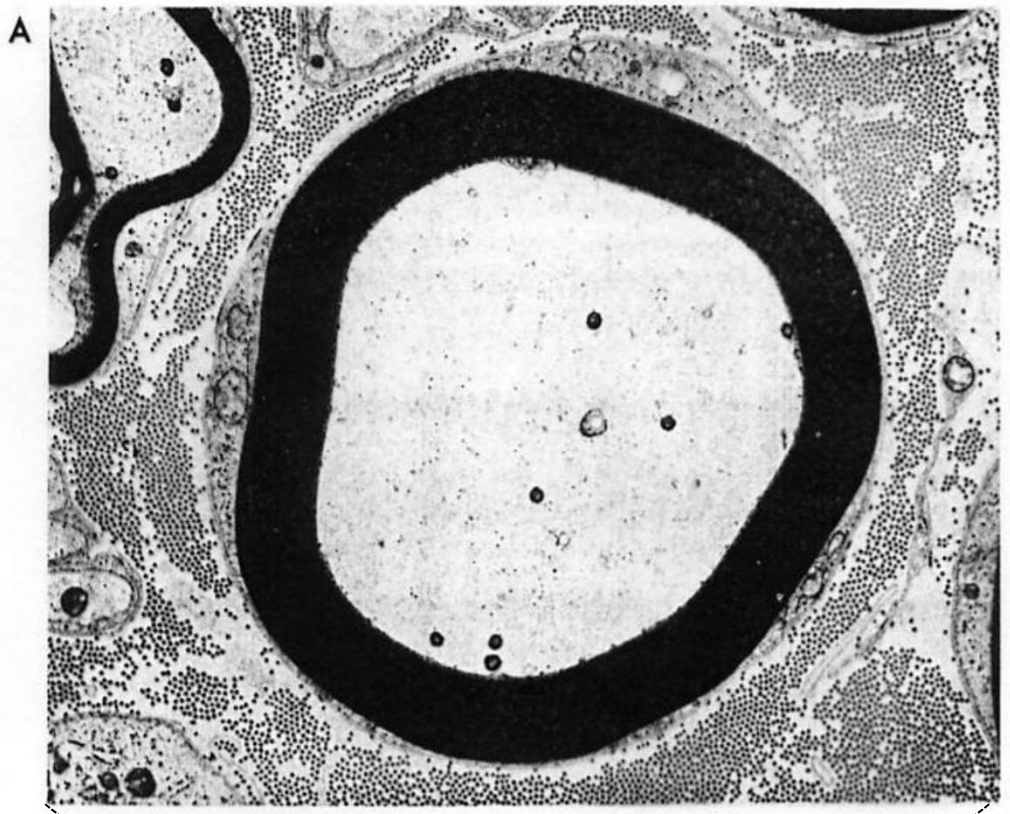


Classification of Sensory Nerve Axons

axons innervating:					
skin	muscle & joint	viscera	examples	myelin	CV (m/sec)
	Group I		muscle spindles	yes	70 - 120
Aβ	Group II		RA/SA mechano. nociceptors	yes	25 - 75
Aδ	Group III	Aδ	nociceptors	yes	5 - 25
C	Group IV	C	nociceptors *	no	< 2.0

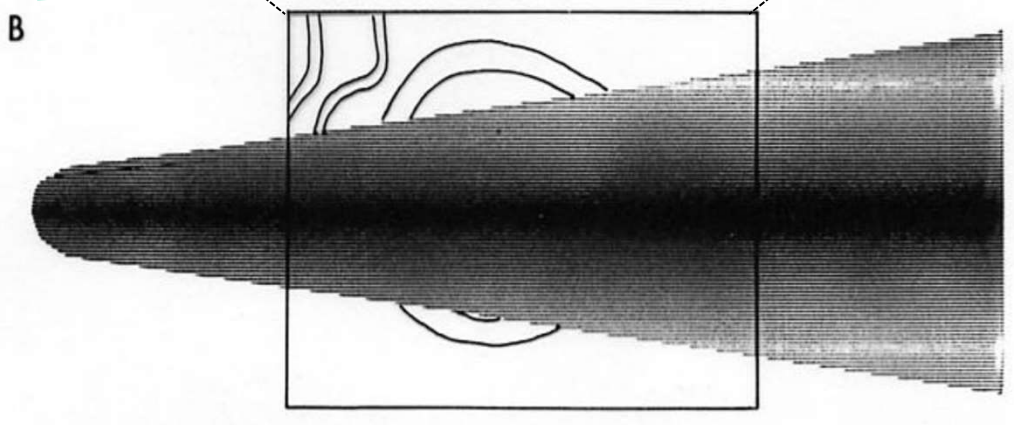
* ~ 10% of C-fibers in sensory nerves are sympathetic efferents

9.5 µm myelinated axon



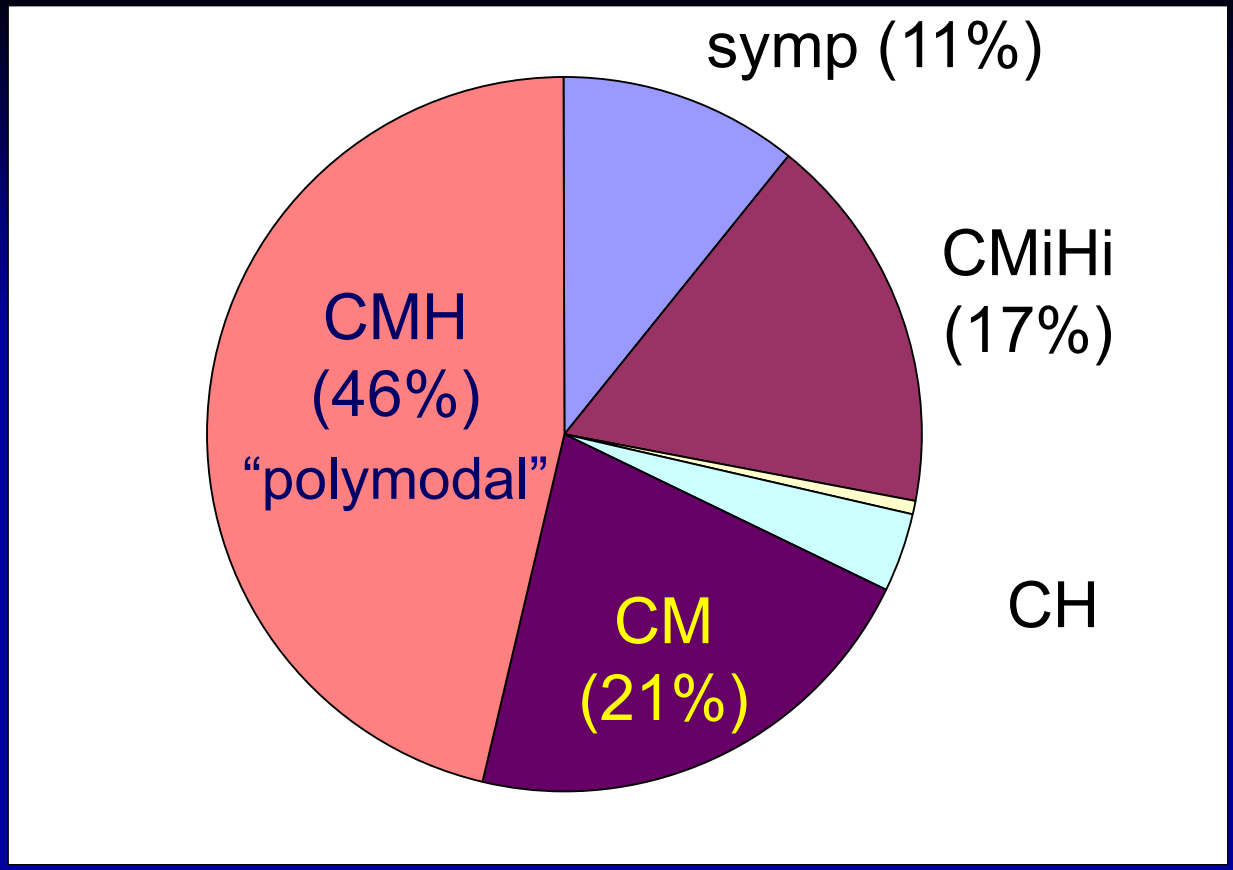
30 µm exposed metal

2 µm electrode tip diameter



Sensations Produced by Intraneural Microstimulation in Humans

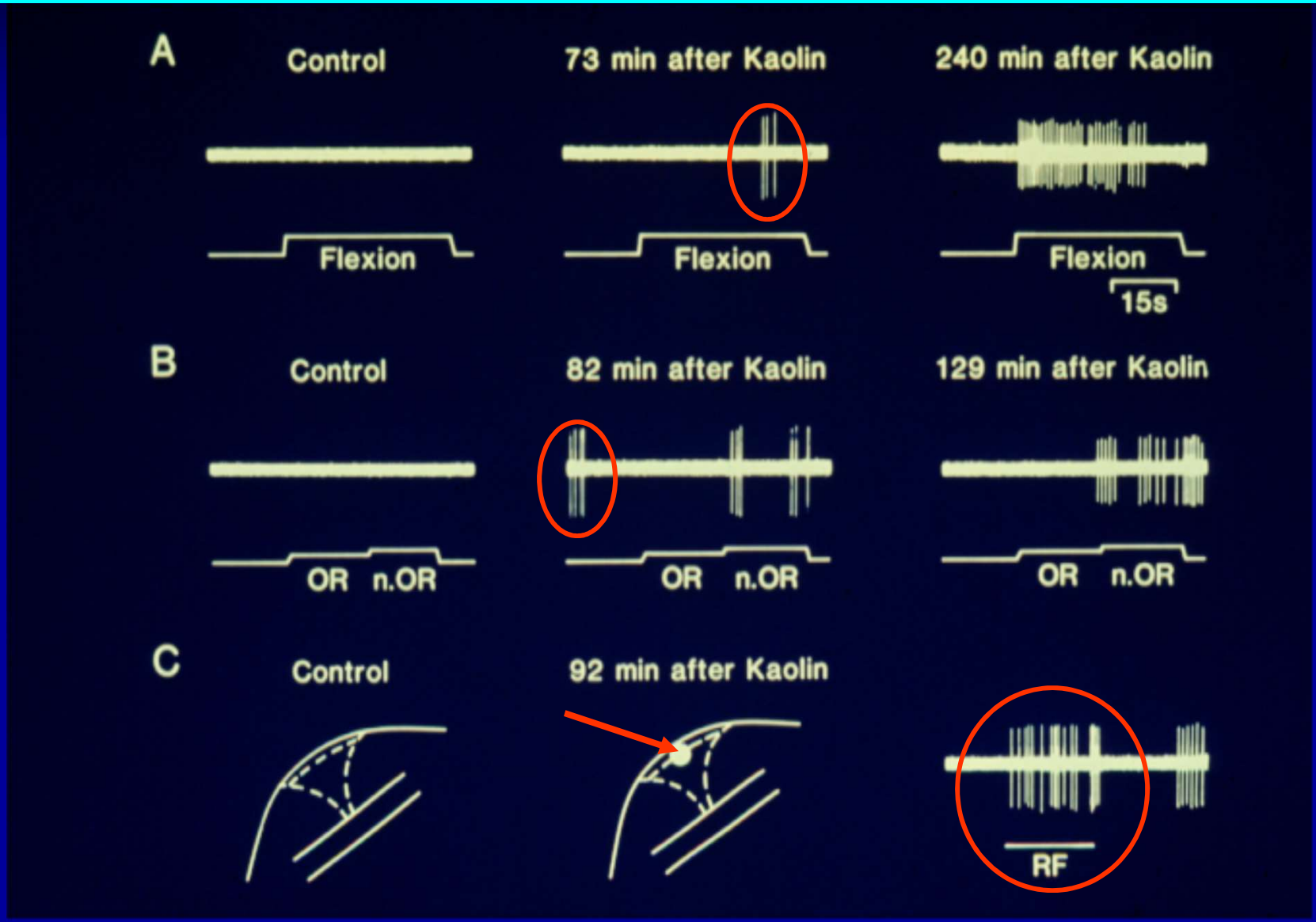
receptor	sensation produced
FA I (Meissner's corpuscle)	tapping at 1Hz, flutter at 10Hz and vibration at 50Hz
FA II (Pacinian corpuscle)	tickle/vibration over 20 - 50Hz
SA I (Merkel's disk)	sustained pressure over 5 - 10Hz
SA II (Ruffini endings)	no sensation ?
A – ultrafast HTMR	Sharp/pinprick pain
A δ mechanical nociceptors	sharp pain
C polymodal receptors	dull, burning pain or itch
muscle nociceptor (group IV)	cramping pain
MIAs	none ?



Relative proportions of 220 C units in cutaneous fascicles of the human peroneal nerve

(Torebjork, Schmelz & Handwerker in *Neurobiology of Nociceptors*, 1996)

What's a 'silent' (mechanically insensitive) nociceptor?



Schiable and Schmidt, 1985

Nociceptors with Aβ fibers

Table 1
Comparison of the reported incidence of Aβ nociceptors in a variety of species

Species	Age	Temperature (core or nerve)	Aδ/Aαβ border used (m/s)	Main D hair upper CV (m/s)	Aβ HTM/A-nociceptive (%)	Peripheral nerve (PN) or dorsal root (DR); cell/fiber	Aδ/Aαβ borderline based on	Reference
Monkey	Young 5–7 kg	Core 38 °C	30		18	PN fiber	Distribution of CVs	Treede et al. [65]
Cat	Young	Nerve 36.5 °C	30	30	38	PN fiber	D hair CVs	Burgess et al. [5]
Cat	Young 2–3 kg	Nerve 36.5 °C	30	30	30	PN fiber	D hair CV CAP	Burgess and Perl [4]
Cat	Not stated	?	36	34	22	PN cell	Not stated	Koerber et al. [31]
Rat	5–8 w 120–180 g F	37 °C	8–14	–	No sensory properties	PN soma	Distribution of CVs	Harper and Lawson [26]*
Rat	Adult 200–400 g	Core 36–37 °C	15?	<15	~48	PN fiber	D hair CVs	Lynn and Carpenter [44]
Rat	Young 5 w	Core temp "physiological"	14	~14	~65	PN cell	Referred to papers	Ritter and Mendell [55]
Rat	7 w, 150–180 g, F	Nerve 30 °C	6.5	6.5	64	DR cell	CAPs	Fang et al. [19]
Guinea pig	Young 1–2 w 130–220 g, F	Nerve 30 °C	4	4	48	DR cell	CAPs, D hair CVs	Lawson et al. [38]
Guinea pig	Young 1–3 w 150–300 g, F	Nerve 30 °C	4.2	4.2	50	DR cell	CAPs, D hair CVs	Djouhri et al. [15]
Mouse	Adult 5–32 w	32 °C	10	7	25%>10 m/s, 50%>7 m/s	PN fiber	D Hair CV CAPs	Koltzenburg et al. [33]

Human 20-49 core 30 30 11

distribution of CVs means that although sensory properties were not determined, the borderline was inferred from CV distribution histograms referred to papers: here the borderline used was obtained from Lynn and Carpenter [44] and Harper and Lawson [26]. Available information on age, weight and sex of animals is shown in column 2, and data about animal core temperature or nerve temperature (of the pool in which the nerve conducted) are in column 3. Where both are available, the nerve temperature is used instead of animal core temperature. Note that the Aδ/Aαβ border used (column 4) is close to the "main D hair upper CV" (column 5) except for the mouse, where the fastest D hair CV (10 m/s) was used in the paper, but the top of the main D hair distribution was 7 m/s (Fig. 1). Column 6 gives the percentage of all A-fiber nociceptors that conducted in the Aβ range.

(Djouhri and Lawson, 2004)

Nociceptor Characteristics

Is it possible to identify a nociceptor without functional characterization?

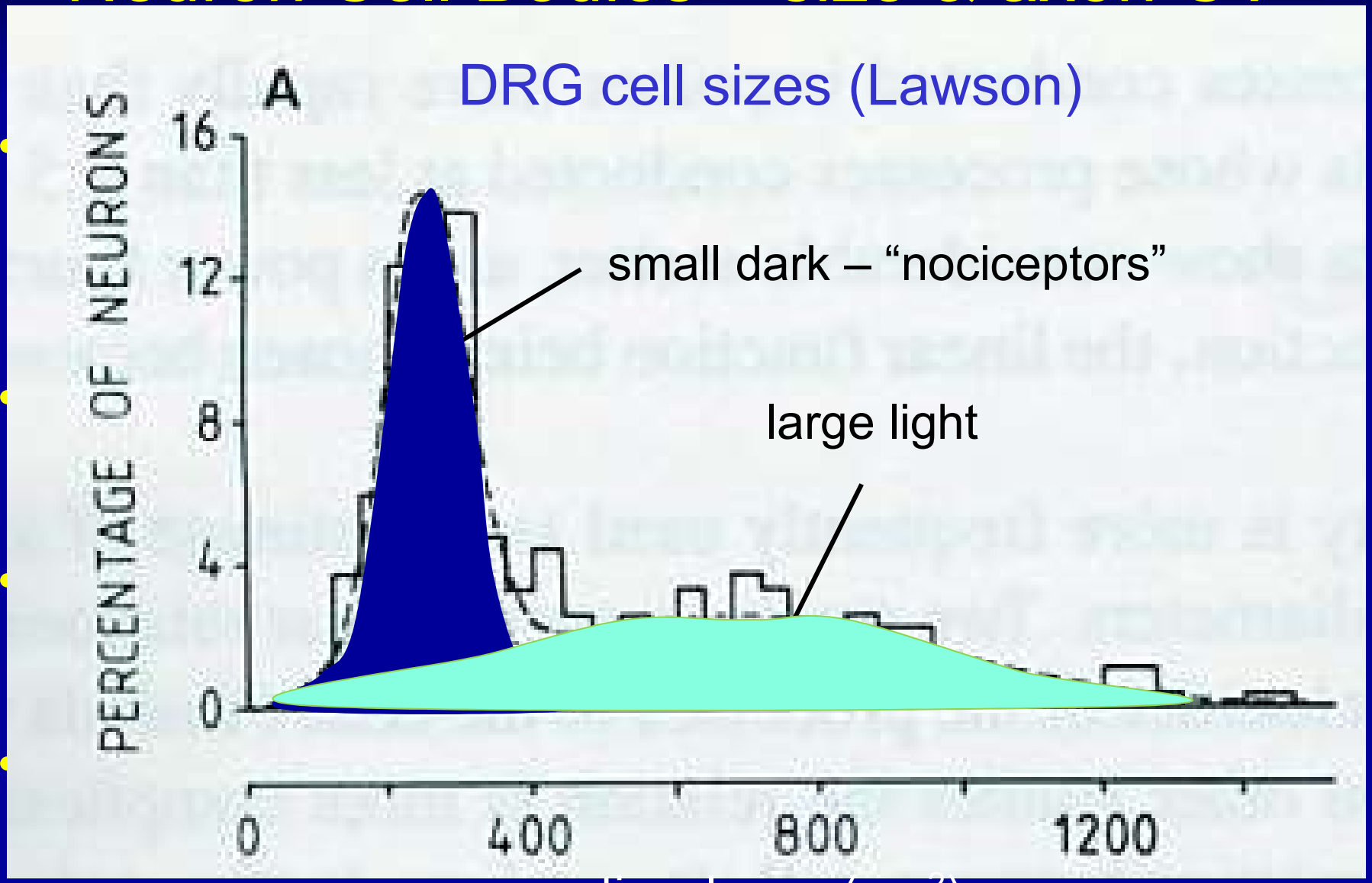
- Cell body size – small *vs* large
- Axon – myelinated or not
- Cell content
  - peptidergic (SP, CGRP)
  - isolectin B4 positive or not
  - growth factors/receptors (e.g., NGF and trkA)
  - nociceptor ‘biomarkers’ (TRPV1, NaV1.8, etc.)

Identification and Classification of Sensory Neuron Cell Bodies/Noci Subpopulations

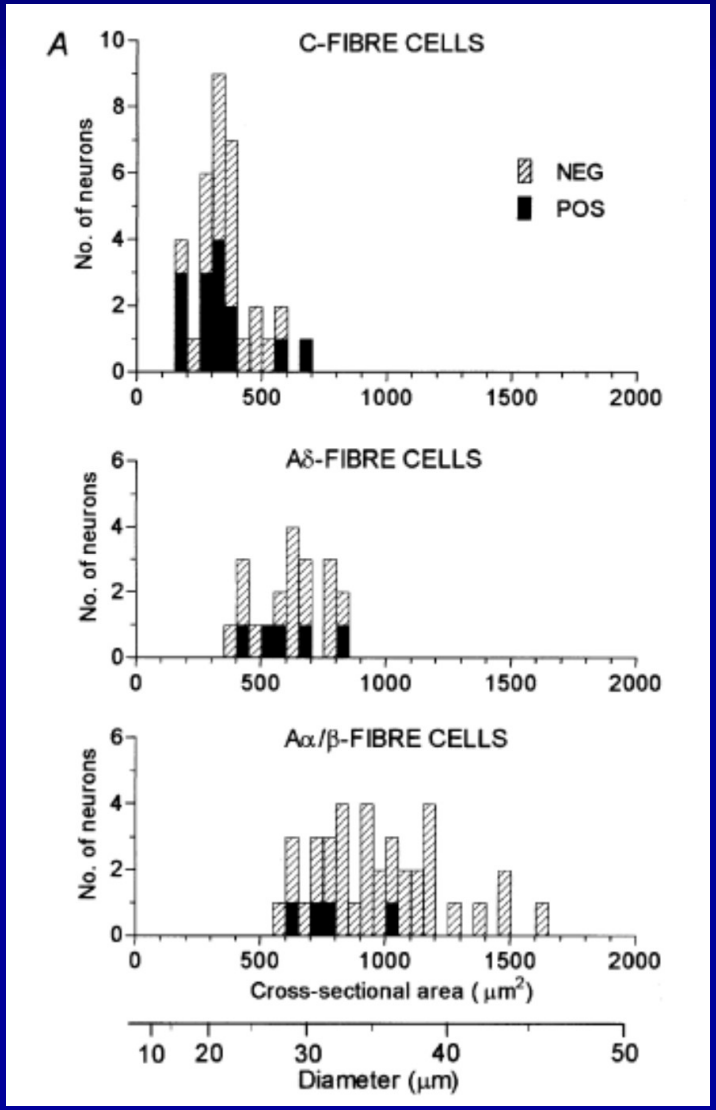
- size
  - large light neurons
  - small dark neurons

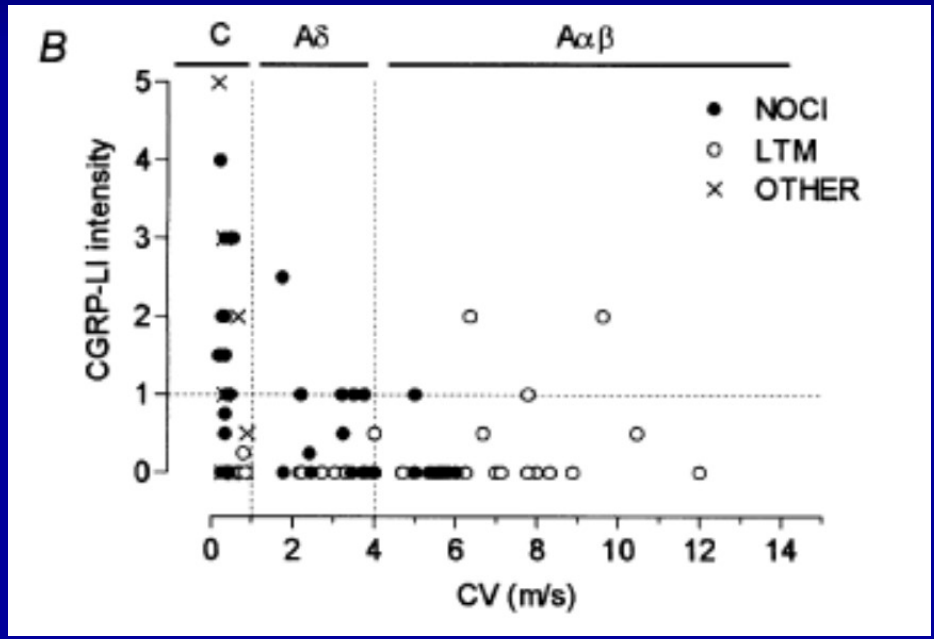
- content
  - neurotransmitter
  - peptides/growth and other factors
  - receptors/ion channels

Identification and Classification of Sensory Neuron Cell Bodies – size & axon CV



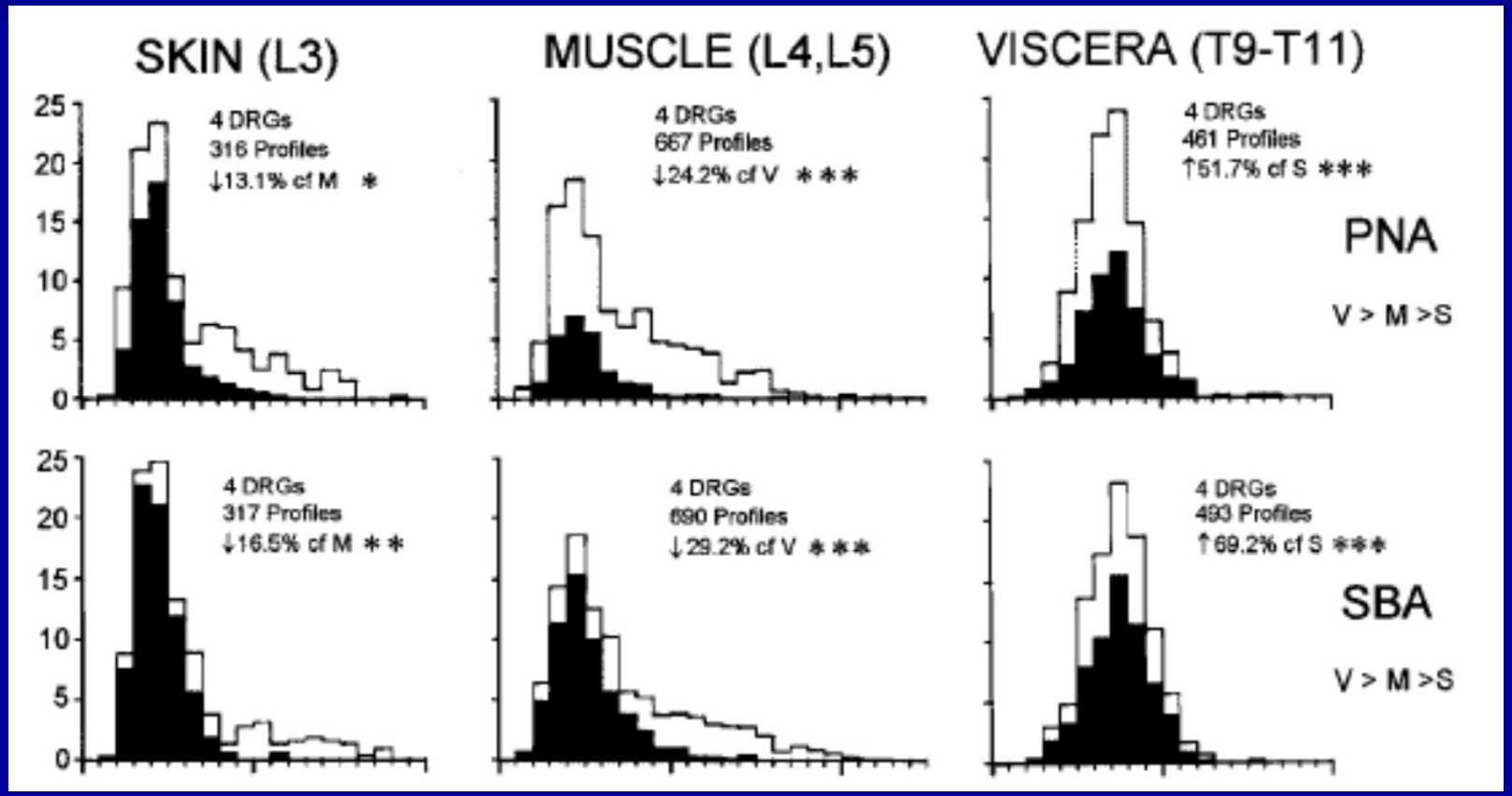
Identification and Classification of Sensory Neuron Cell Bodies – size/axons





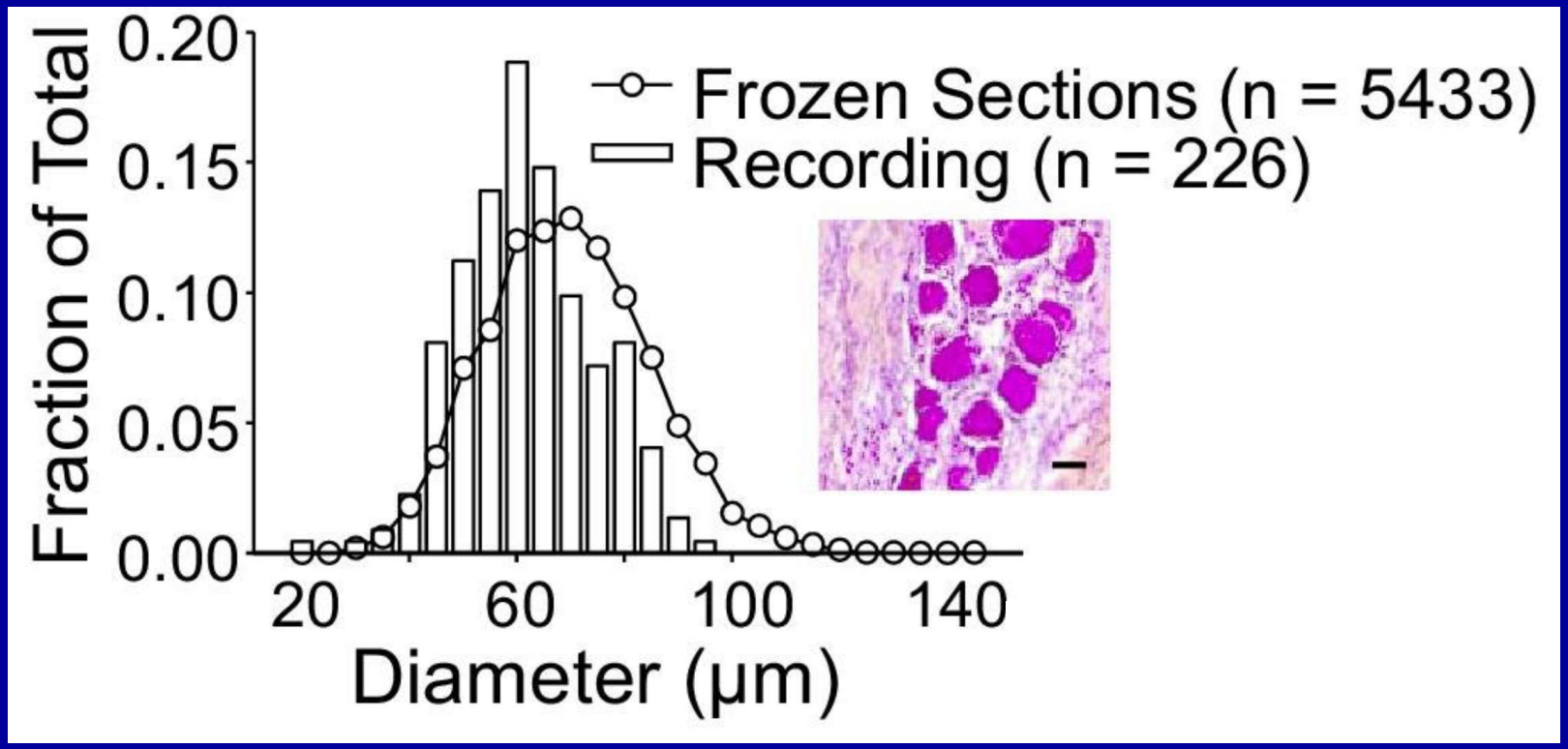
Lawson SN et al (2002) J Physiol 540(3): 989-1002

Identification and Classification of Sensory Neuron Cell Bodies – size/axons



Perry MJ and Lawson SN (1998) Neuroscience 85(1): 293-310

Identification and Classification of Sensory Neuron Cell Bodies – size/axons



Zhang XL et al (2017) eLife doi 10.7554/eLife.23235

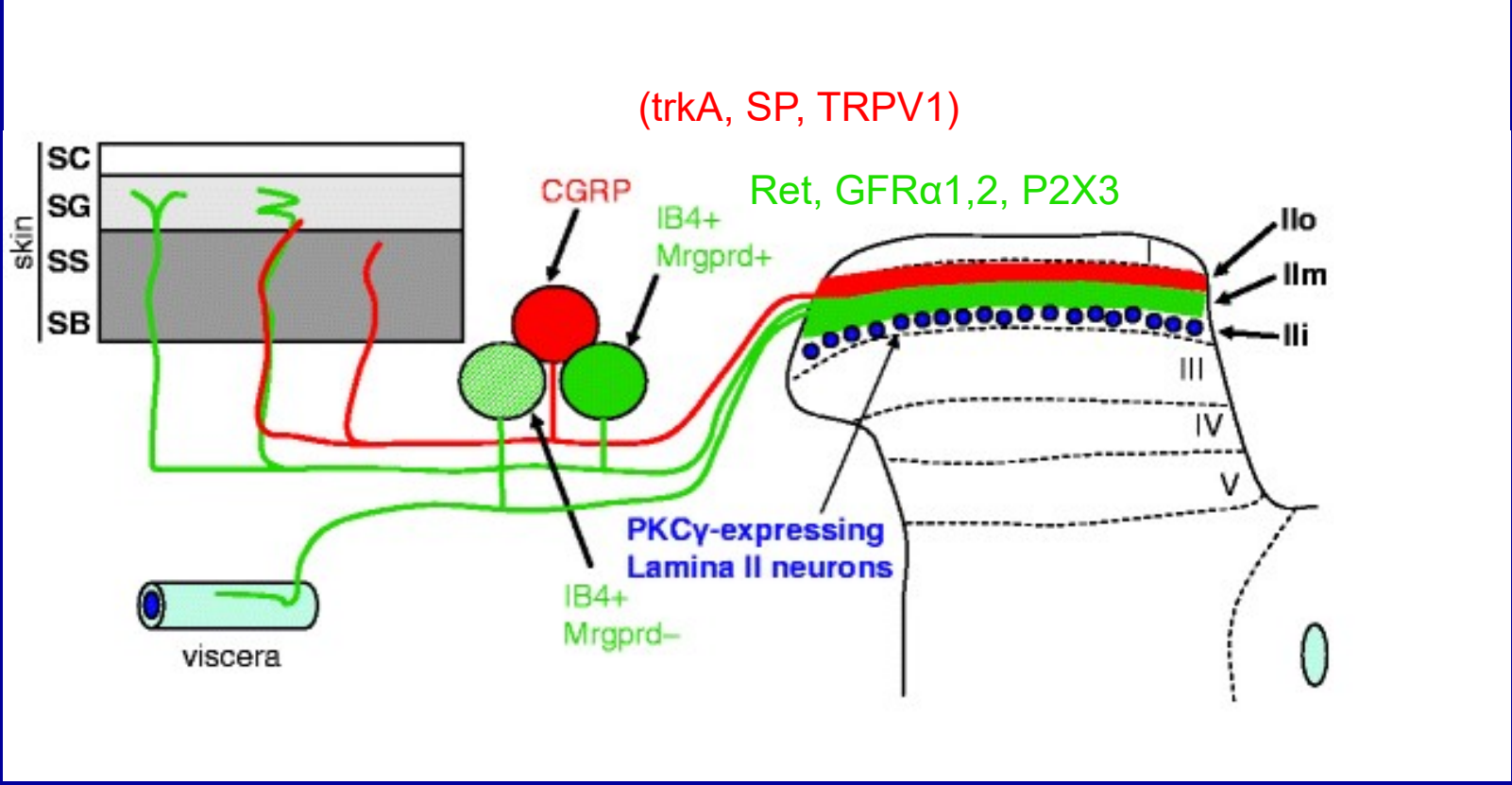
Identification and Classification of Sensory Neuron Cell Bodies – content 1

- substance P: both C-fiber and Aδ-fiber DRG cells contain substance P
- CGRP: many CGRP containing DRG cells also contain substance P-like immunoreactivity
- somatostatin
- adenomedullin
- vasoactive intestinal polypeptide (VIP)
- galanin
- enzymes (e.g., TH)

Identification and Classification of Sensory Neuron Cell Bodies – content 2

- ionotropic receptors:
  - serotonergic - $5\text{-}HT_3$
  - purinoceptive - $P2X_2$, $P2X_3$ and $P2X_{2/3}$
  - ASICs (acid-sensing ion channels)
  - voltage-gated Na^+ ($Na_V1.7$, $Na_V1.8$ $Na_V1.9$), K^+ and Ca^{++} channels
  - transient receptor potential (TRP) family - TRPV1, V4, TRPA1, TRPM3, M8
- Metabotropic receptors
- Growth factor receptors

IB4 Binding to Identify Noci Subpopulations



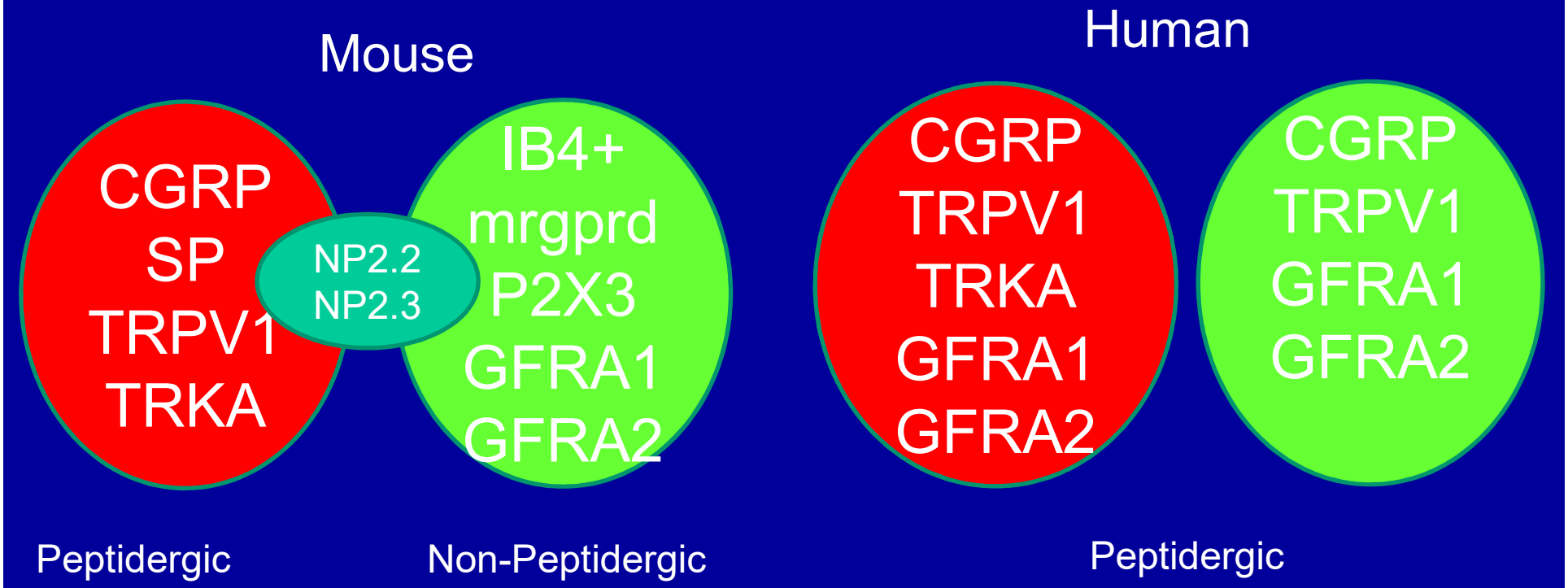
Gereau R and Cavallone LF (2013) Chapter 16: Anesthetic Pharmacology. Evers, Maze, and Kharasch Eds

TH cluster – express tyrosine hydroxylase (*Th*) ~ distinct subclass of unmyelinated neurons

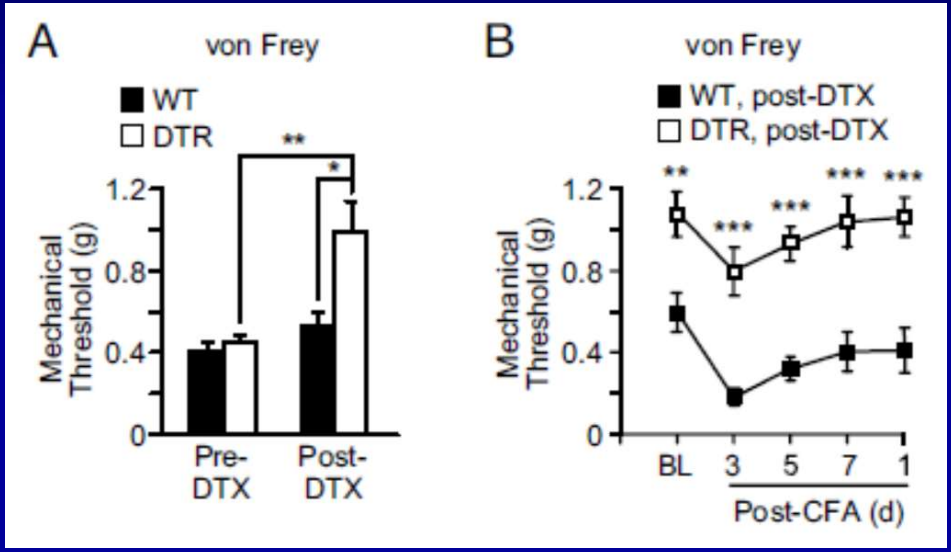
Unbiased classification of sensory neuron types by large-scale single-cell RNA sequencing

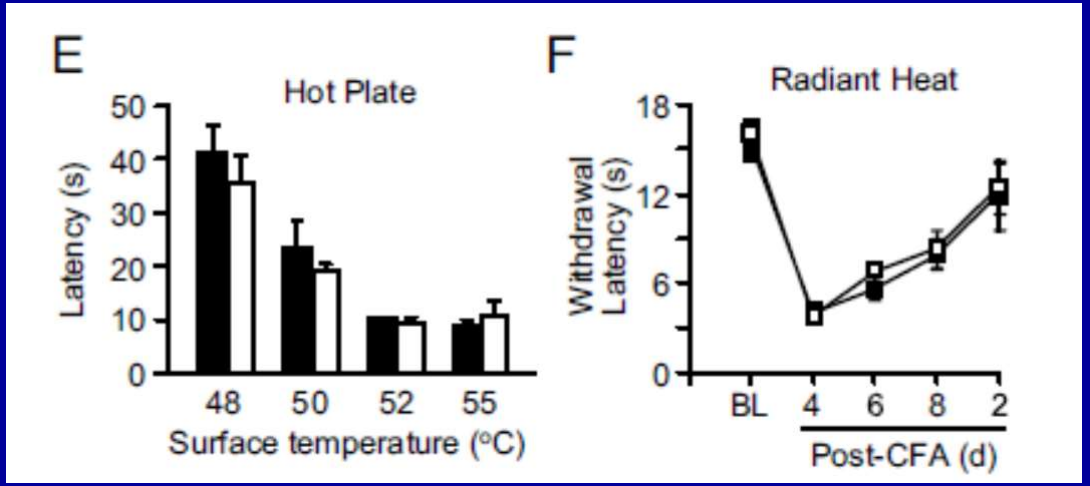
Usoskin, et al. *Nature Neurosci* 2015

Species Differences?



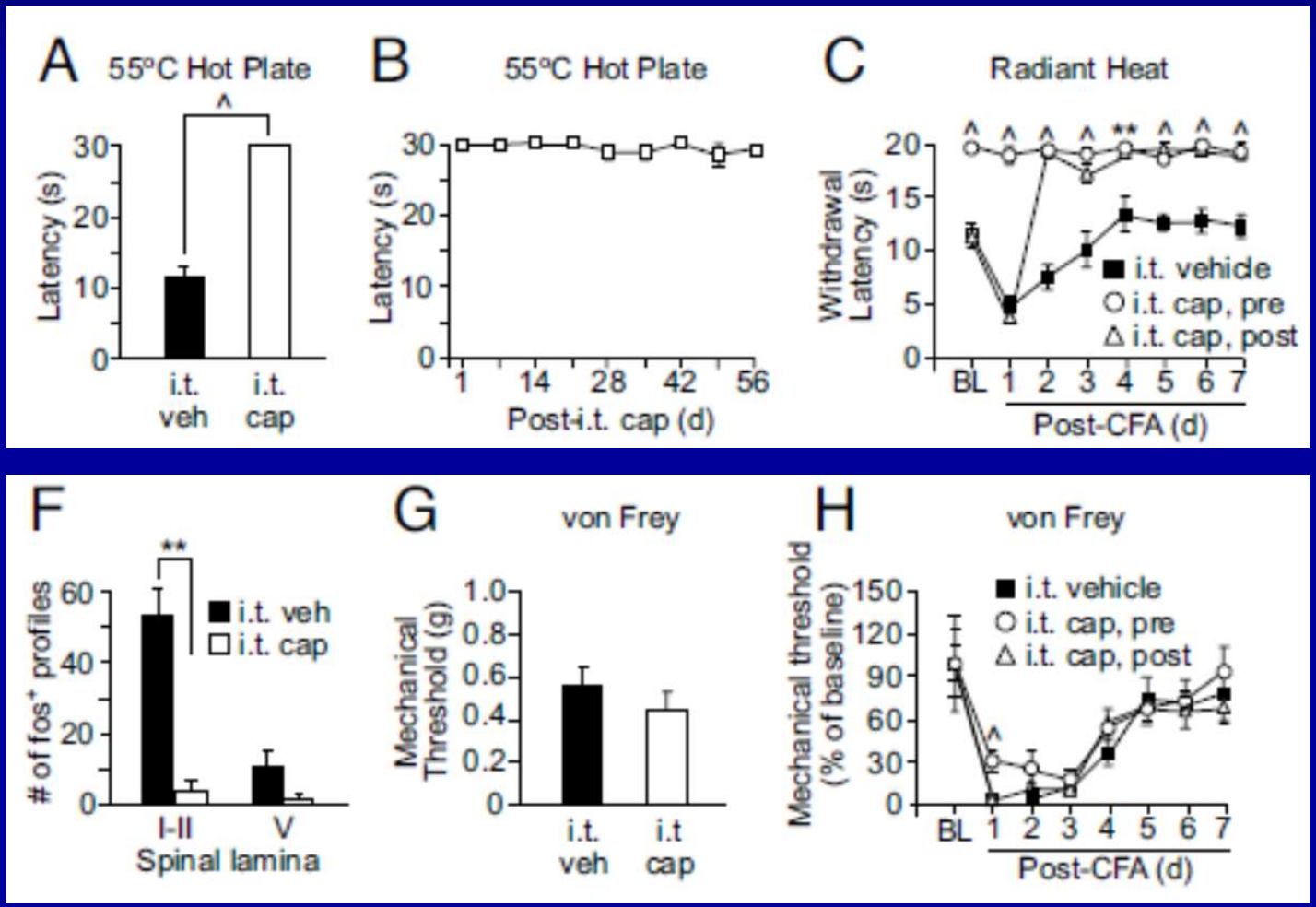
Functional Implications?





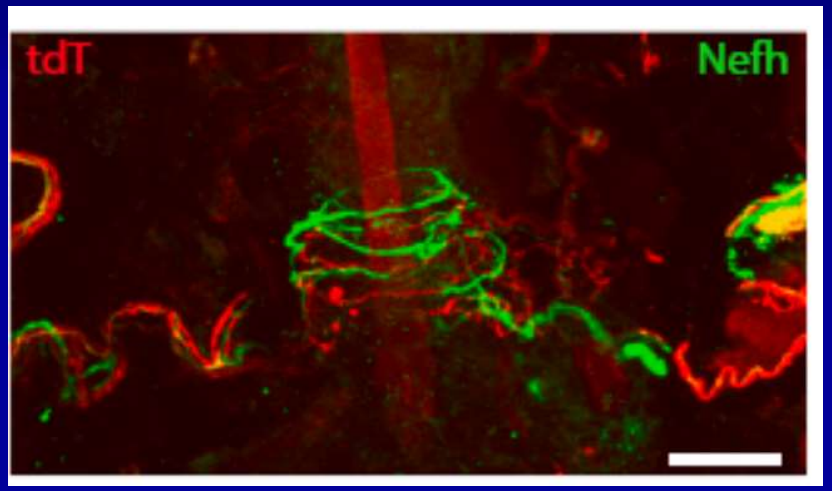
Cavanaugh DJ et al (2009) PNAS 106(22): 9075-80

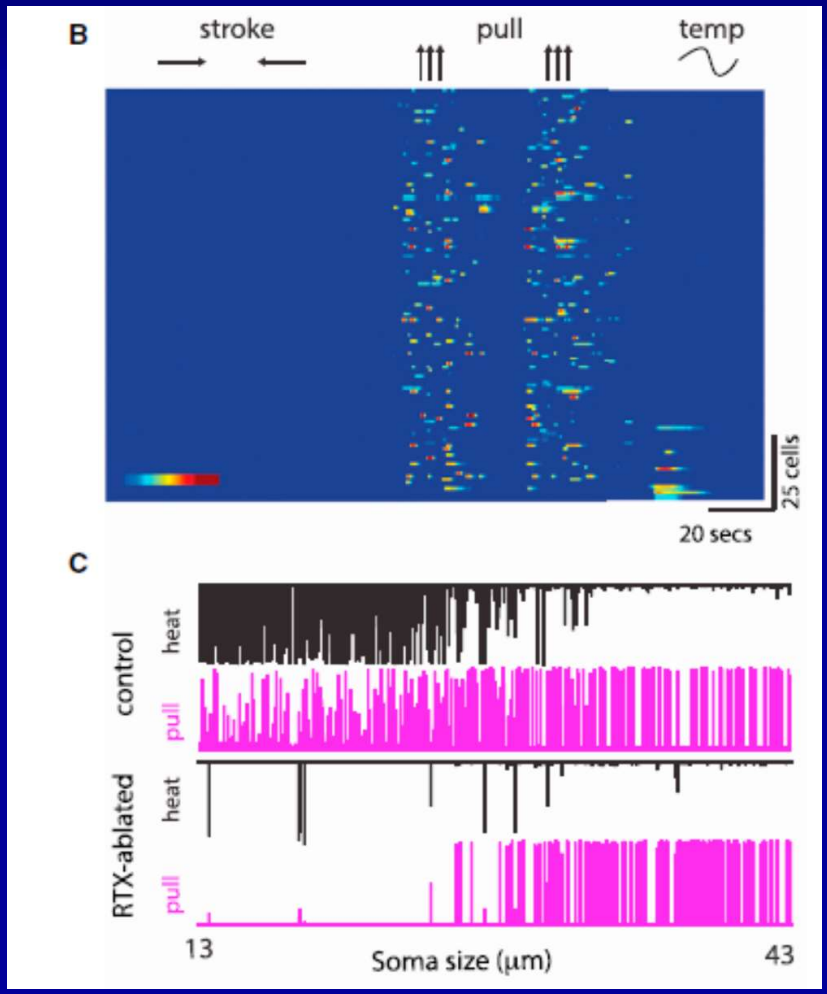
Functional Implications?



Cavanaugh DJ et al (2009) PNAS 106(22): 9075-80

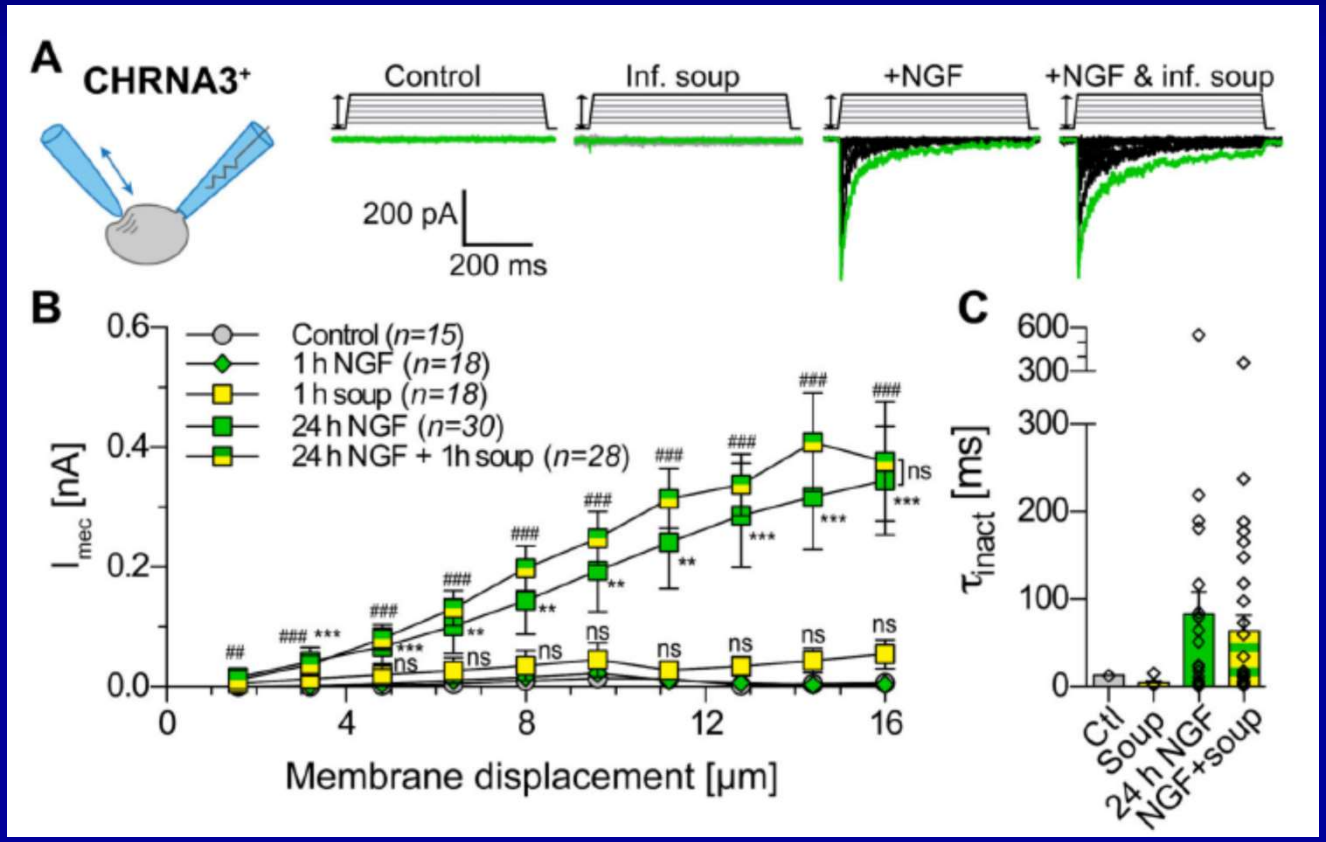
Functional Implications?





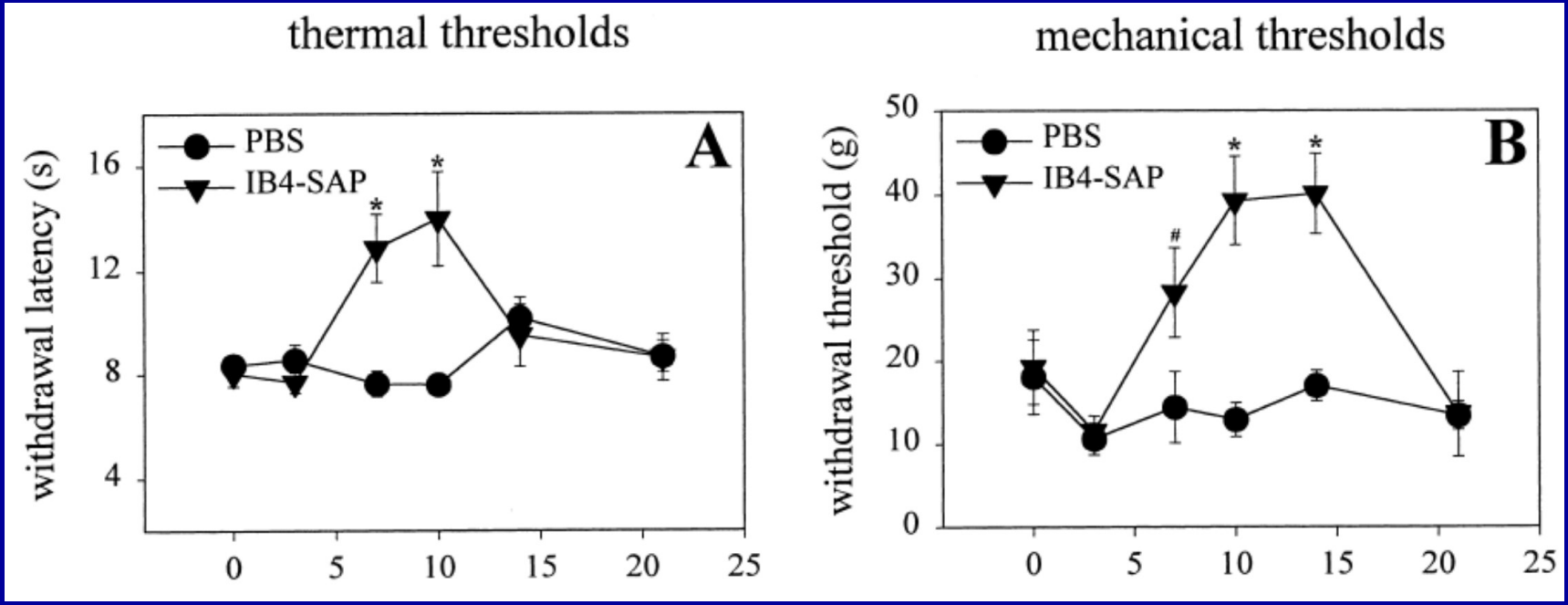
Ghitani N et al (2017) Neuron 95: 944-54

Functional Implications?



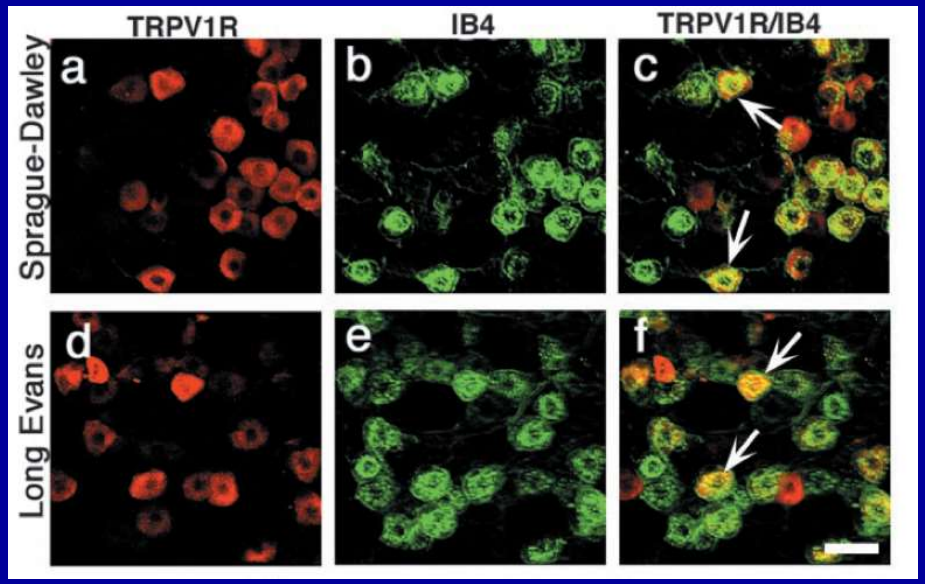
Prato V et al (2017) Cell Rep 21(11): 3102-15

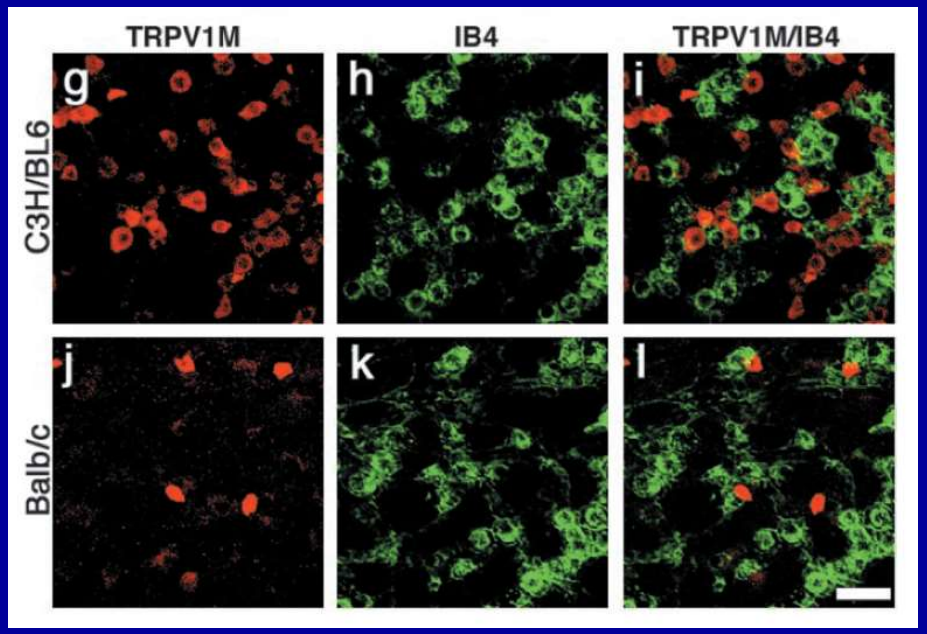
Species Differences



Vulchanova L et al (2001) Neuroscience 108(1): 143-55

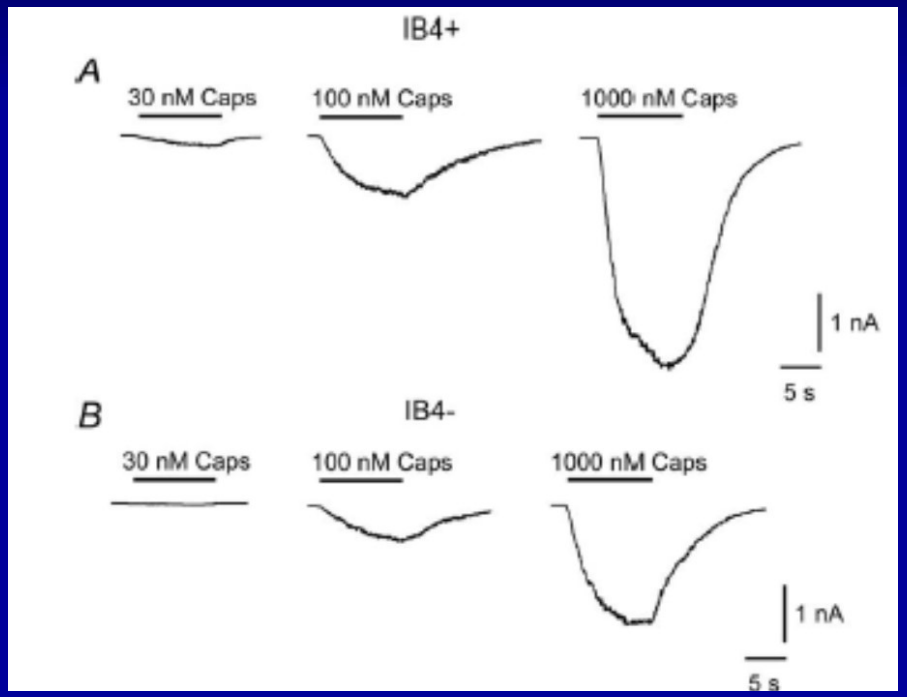
Species Differences

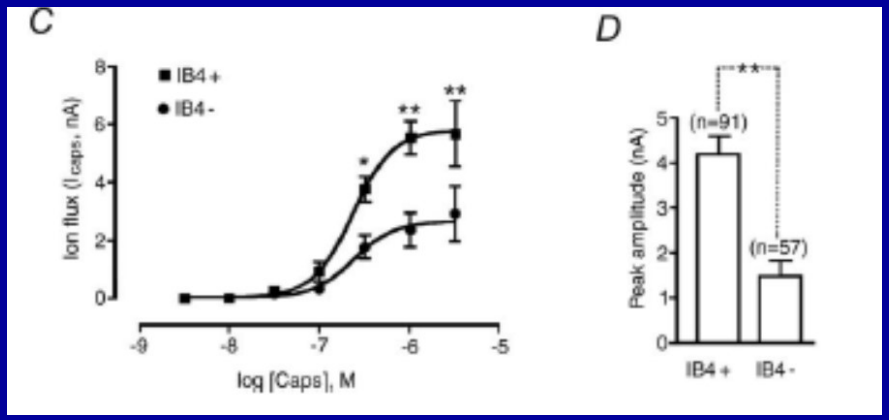




Woodberry J et al (2004) J Neurosci 24(28): 6410-5

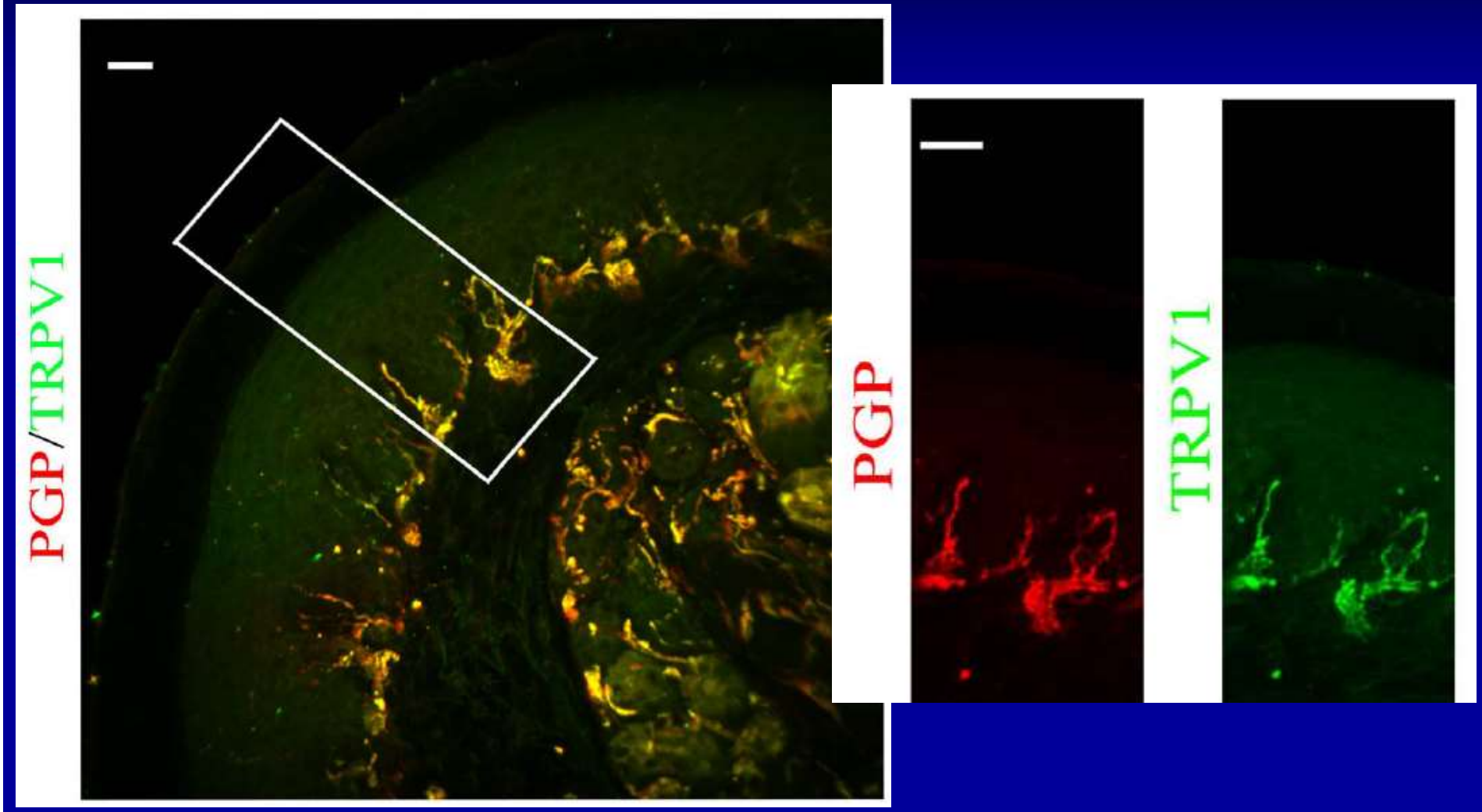
Species Differences





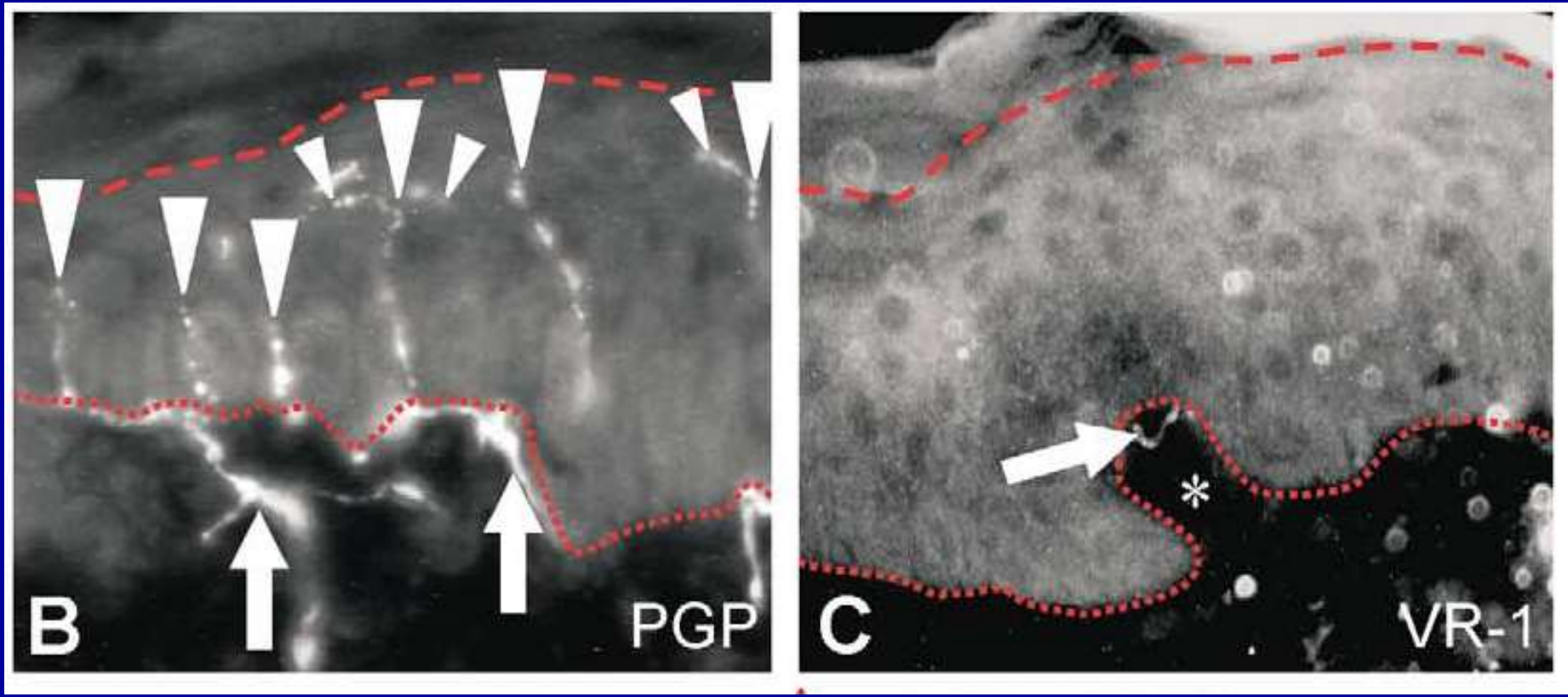
Liu et al (2004) Neuroscience 127: 659-72

Species Differences



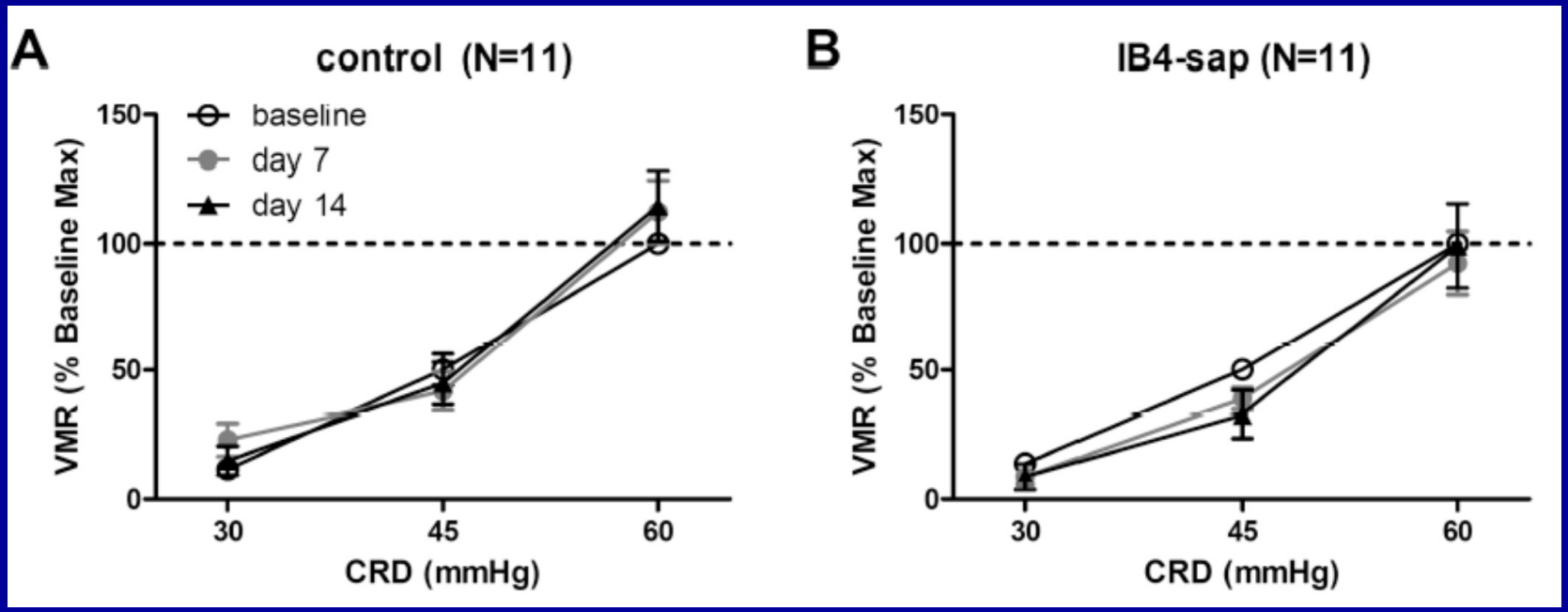
Lakoma J et al (2014) PlosOne 9(10): e108641

Species Differences



Petersen K et al (2002) PAIN 98: 119-26

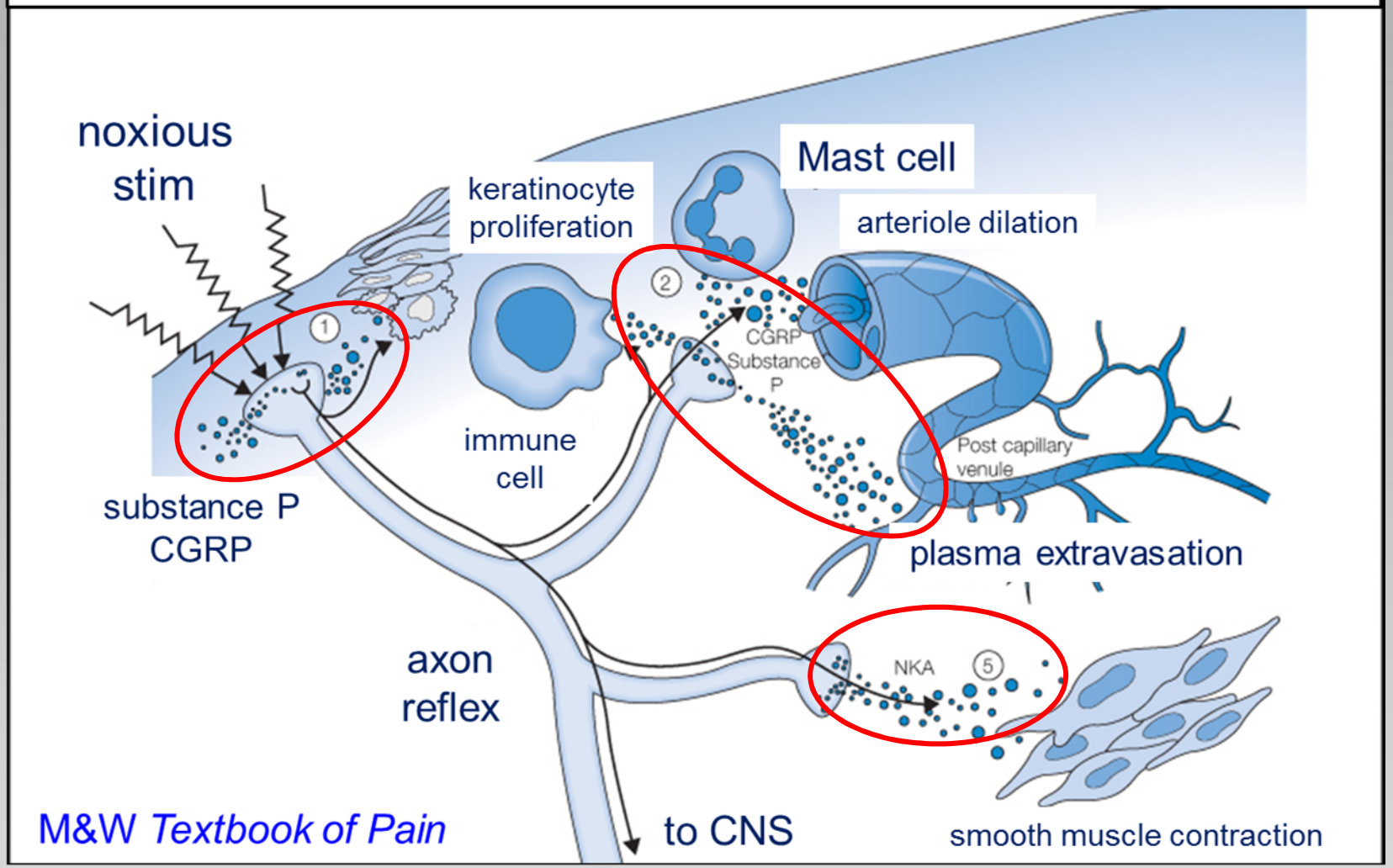
Impact of Target of Innervation



La JH et al (2016) PAIN 157(2): 348-54

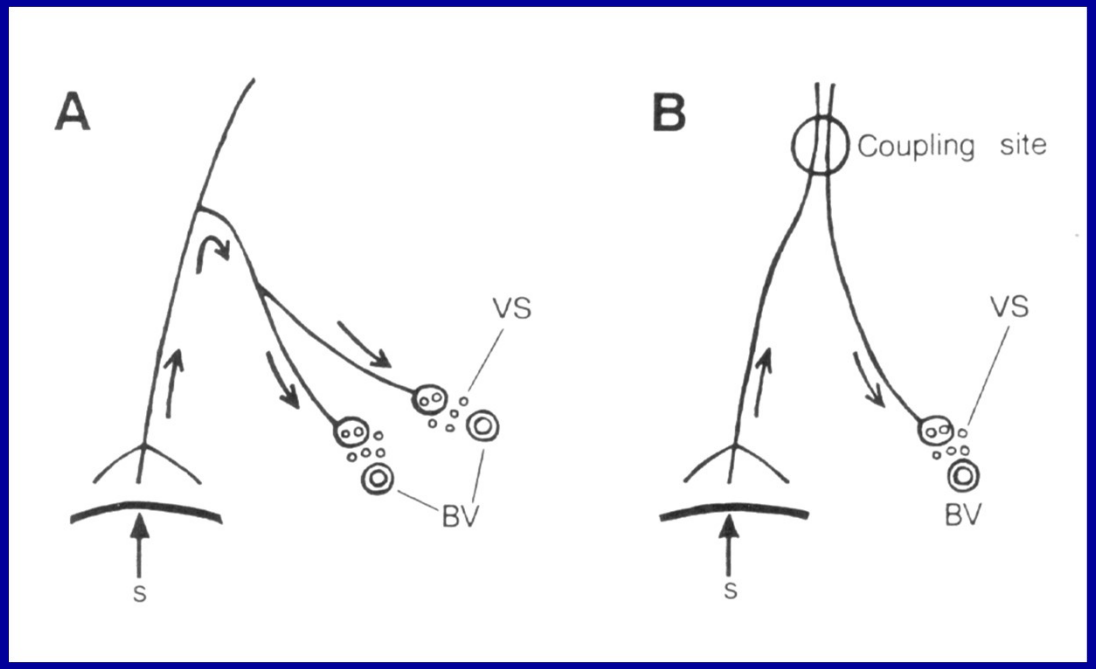
Efferent Function

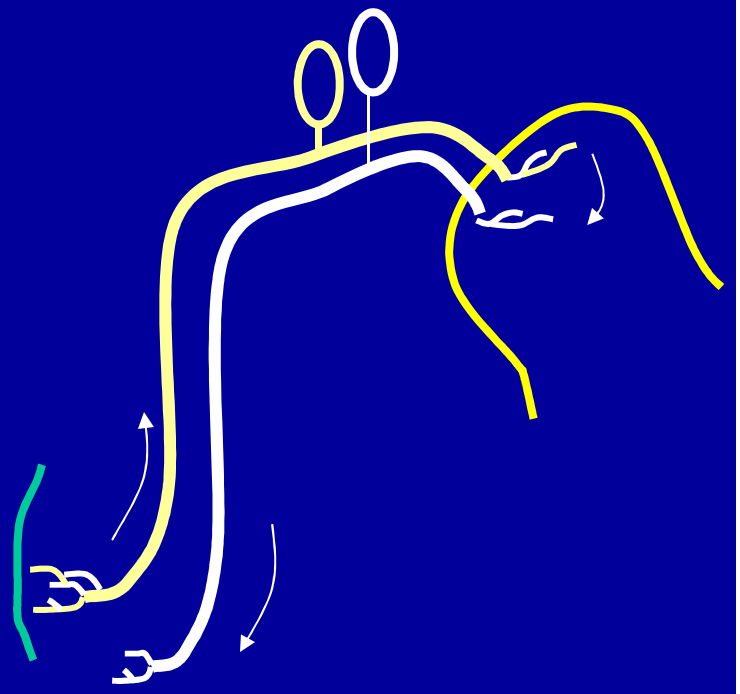
Neurogenic inflammation - an ***efferent*** function of afferent (sensory) nerves (Stricker, 1876; Bayliss, 1901).



Efferent Role of Nociceptors

Mechanisms of Transmitter Release





So, how can you know a nociceptor if you encounter one?

- Nociceptors are identified reliably by *function* – they encode, they sensitize, …
- Be cautious in your interpretation
  - Heterogeneous
  - Species differences
  - Target of innervation differences
  - Impact of age, sex, previous history, genetics

Summary

- Nociceptor activation evokes important protective withdrawal reflexes
- Nociceptors are dynamically involved in many chronic pain conditions
- Subpopulation specific contribution
- Nociceptor properties include:
  - encoding noxious input into the CNS
  - sensitization
  - an efferent function (neurogenic inflammation)
- Nociceptors are defined functionally