
# Psychoneurodermatology

ACVD Resident Seminar

Chie Tamamoto-Mochizuki, DVM, dipAiCVD, Ph.D.

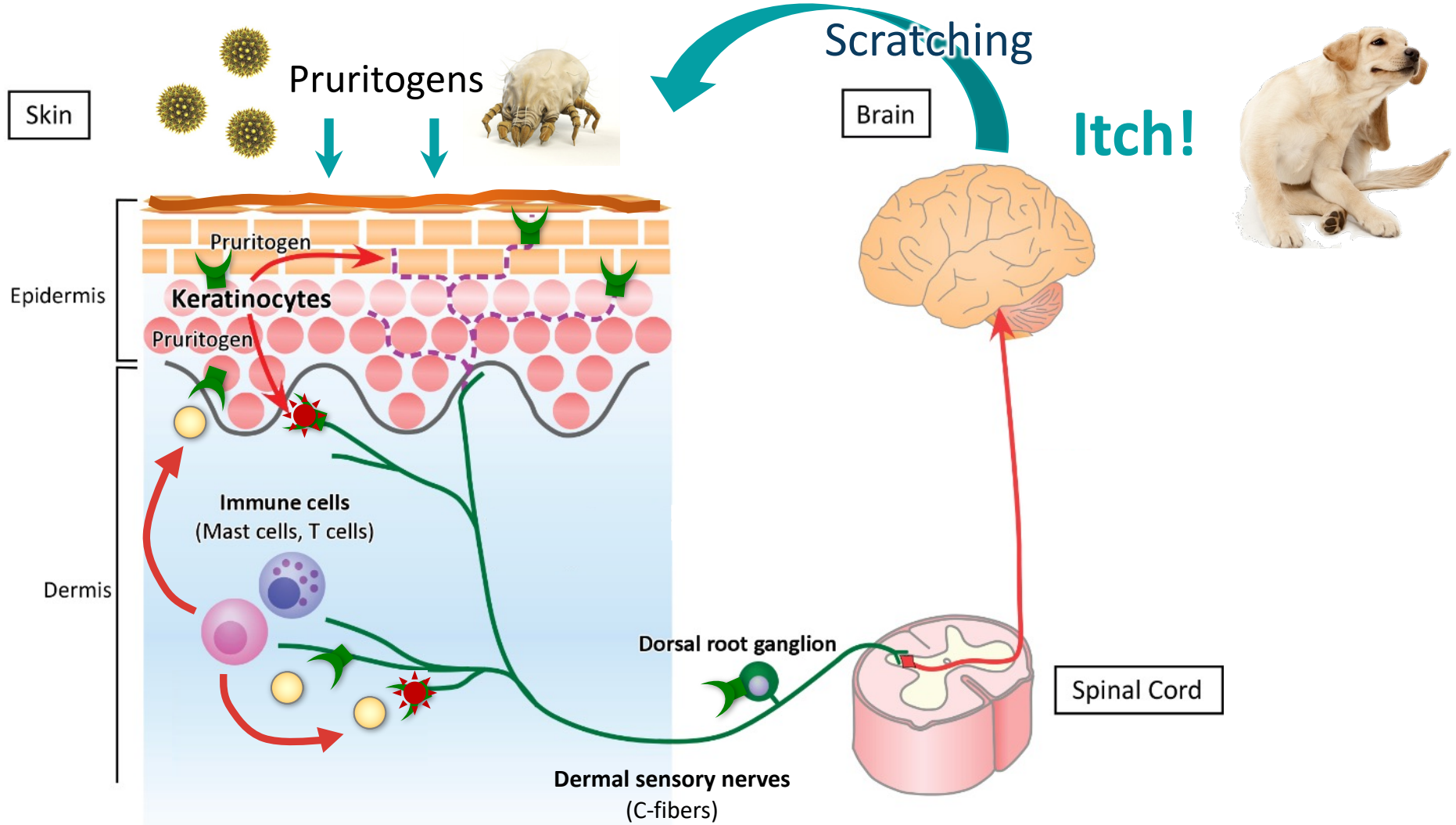
North Carolina State University
Raleigh, NC


# COI Disclosure

CTM has received a Ph.D. scholarship and a research grant from Zoetis

NAVDF

# "*It Is the Brain that Itches, Not the Skin*"



# Pruritus is a *Unique* Sensation

”Itch sensation is limited to skin, mucosa and cornea”


# Learning Outcomes

1. To remember key pruritogens and their receptors
2. To be able to name psychoneurodermatological diseases
3. To be able to explain the mode of actions of drugs targeting neuronal pathways

NAVDF

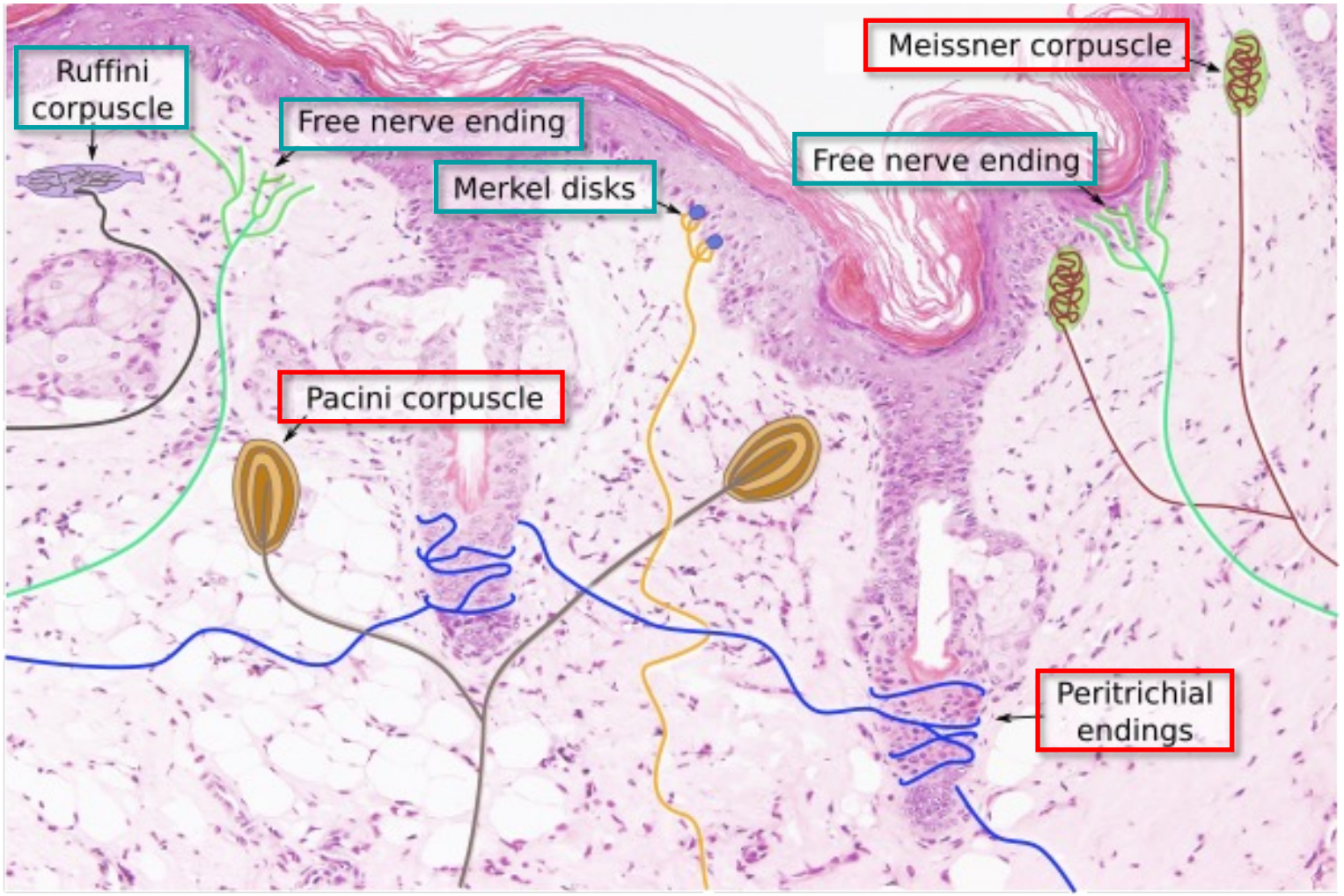

# Outline

1. Neuroanatomy and neurobiology of skin
2. Pathology of pruritus
3. Diagnosis of neuropathic/psychogenic skin diseases
4. Management of neuropathic itch

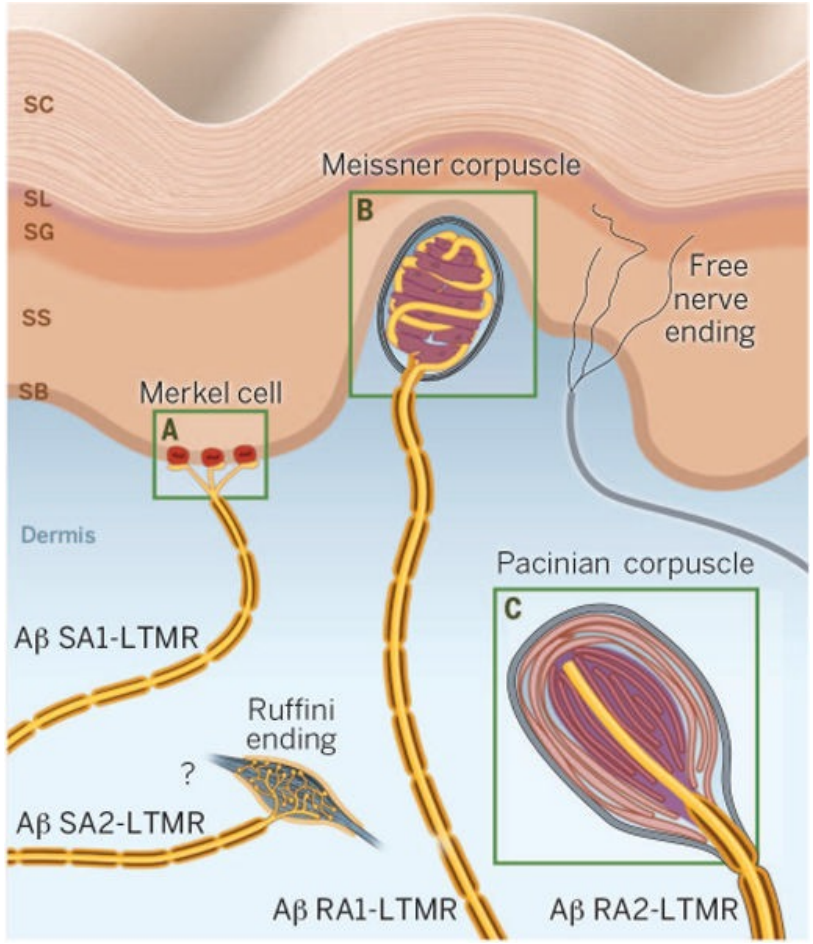
NAVDF

# 1. Neuroanatomy and Neurobiology of Skin

# Cutaneous Sensory Receptors



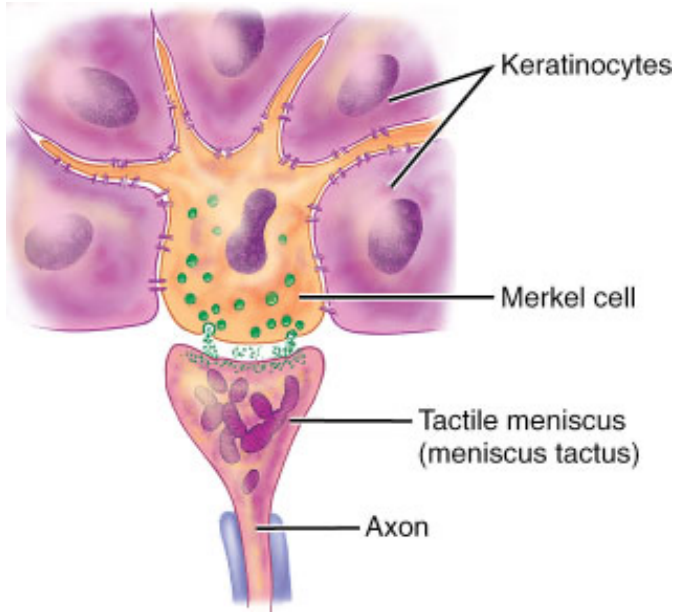
# Mechanoreceptors in Skin

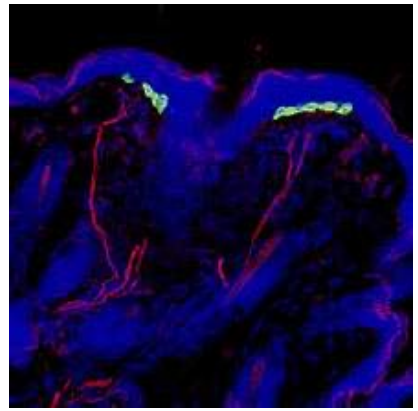



Zimmerman. 2014. *Science*

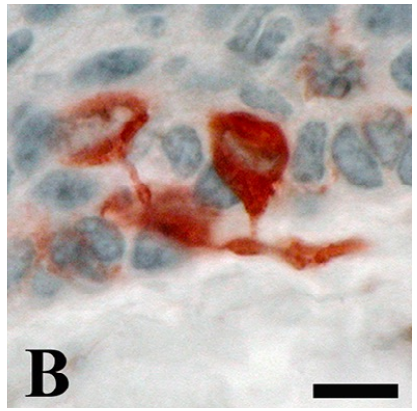
## Merkel cell

- *Light touch*
- Slowly-adopting *Aβ* sensory fiber



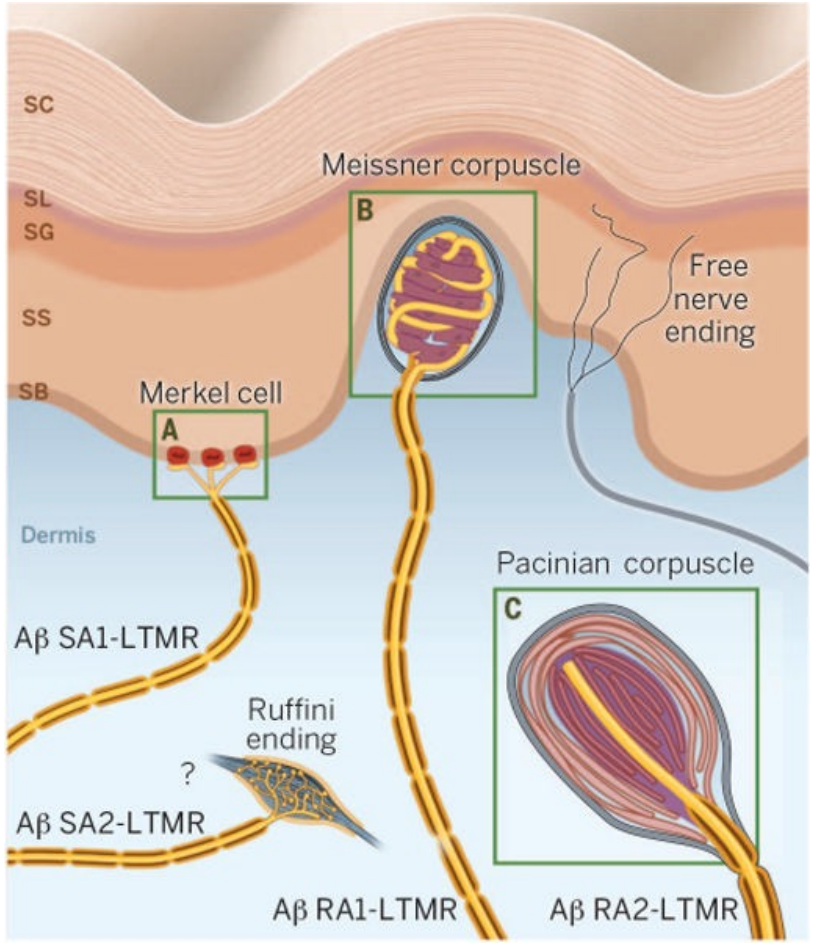
Merkel cells (CK20)
Nerve fibers (red)




Merkel cells (NSE)

Ramírez . 2014. *Res Vet*

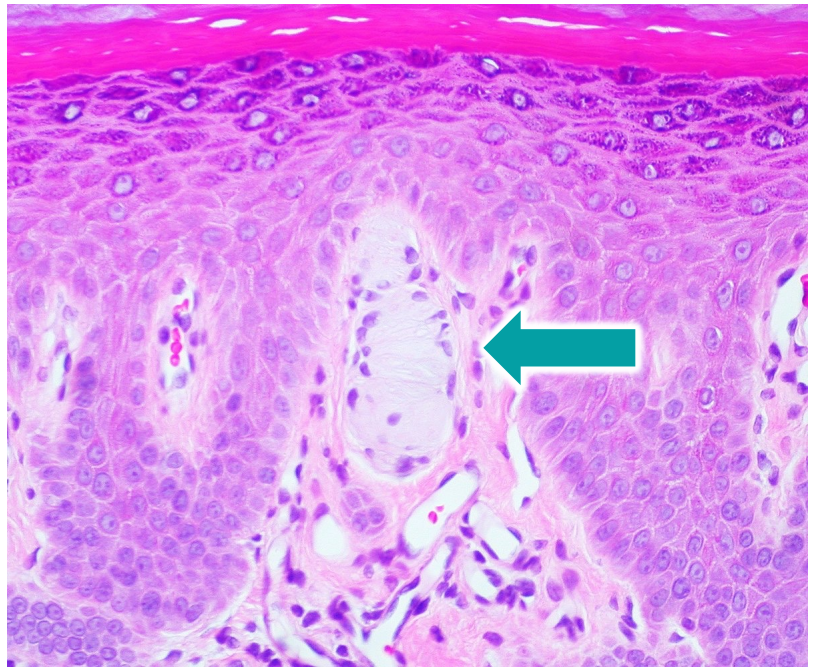
# Mechanoreceptors in Skin



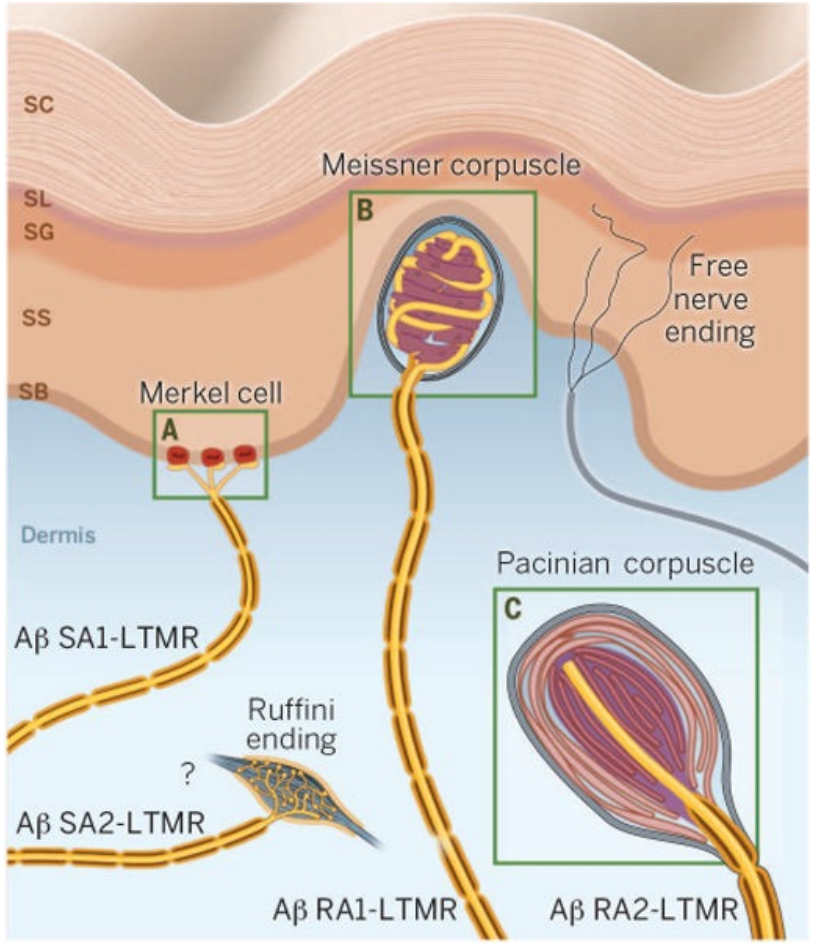

Zimmerman. 2014. *Science*

## Meissner's corpuscle

- *Touch* (dynamic skin deformation)
- Rapidly-adapting *Aβ* sensory fiber



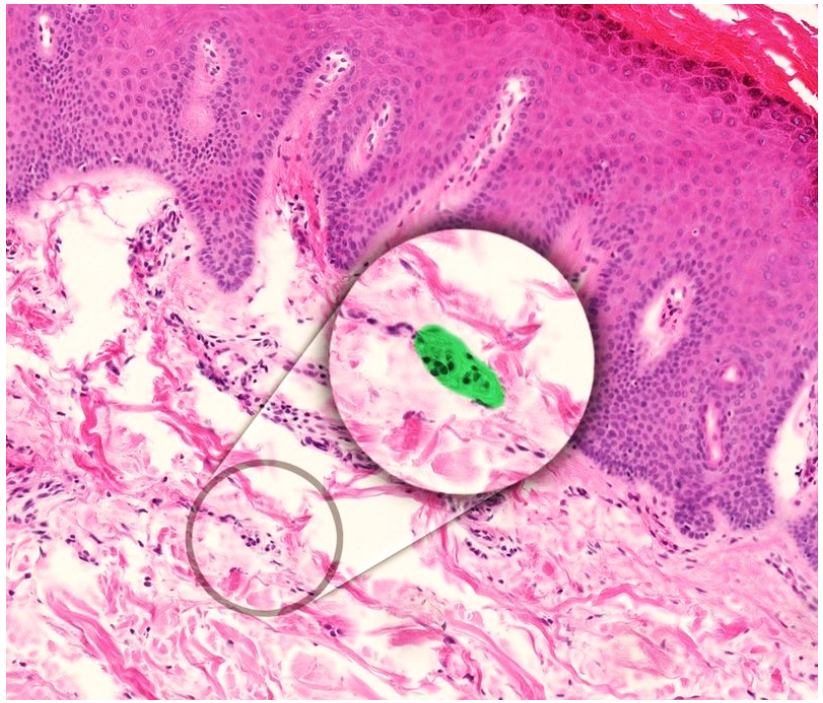
# Mechanoreceptors in Skin



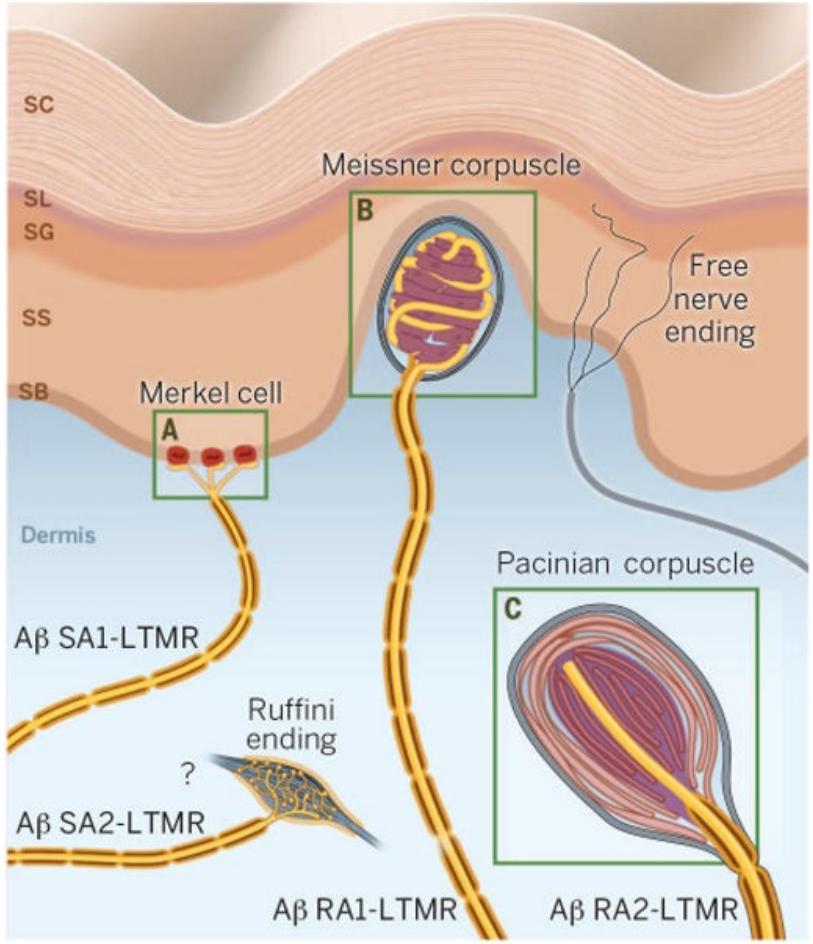

Zimmerman. 2014. *Science*

## Ruffini corpuscle

- *Stretch*
- Slowly-adapting *Aβ* sensory fiber



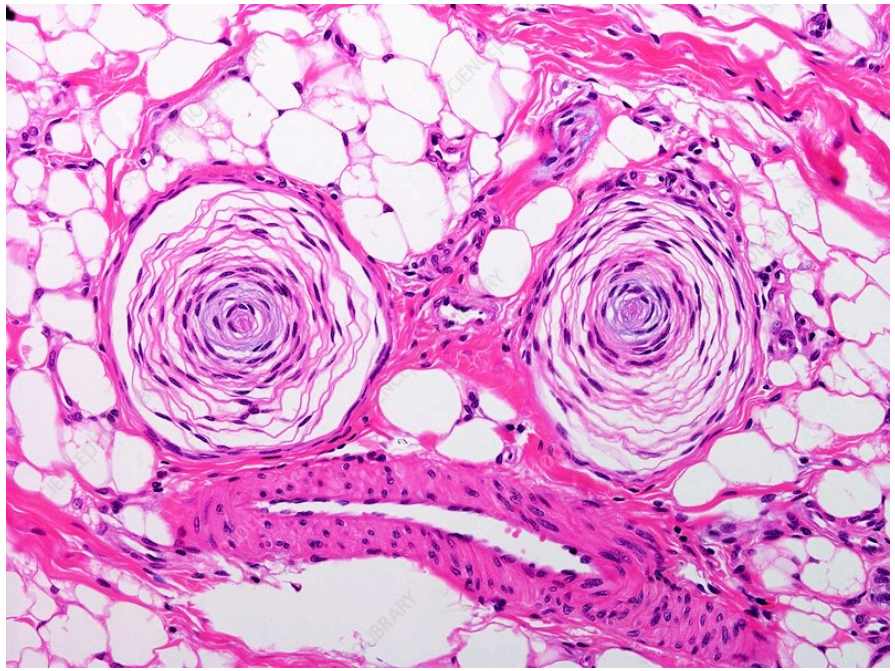
# Mechanoreceptors in Skin




Zimmerman. 2014. *Science*

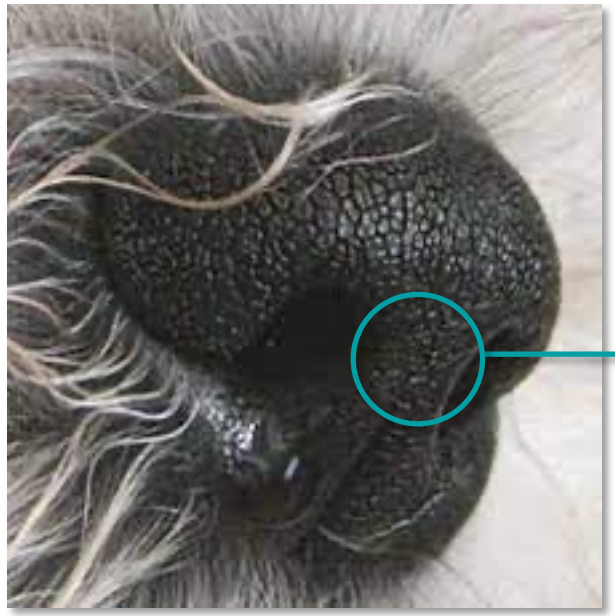
## Pacinian corpuscle

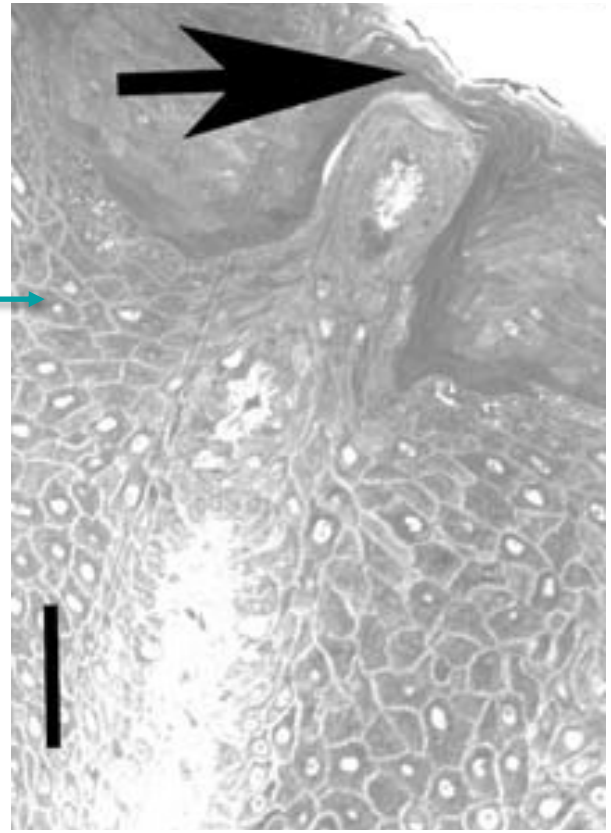
- *High pressure*, *vibration*
- Rapidly-adapting *Aβ* sensory fiber

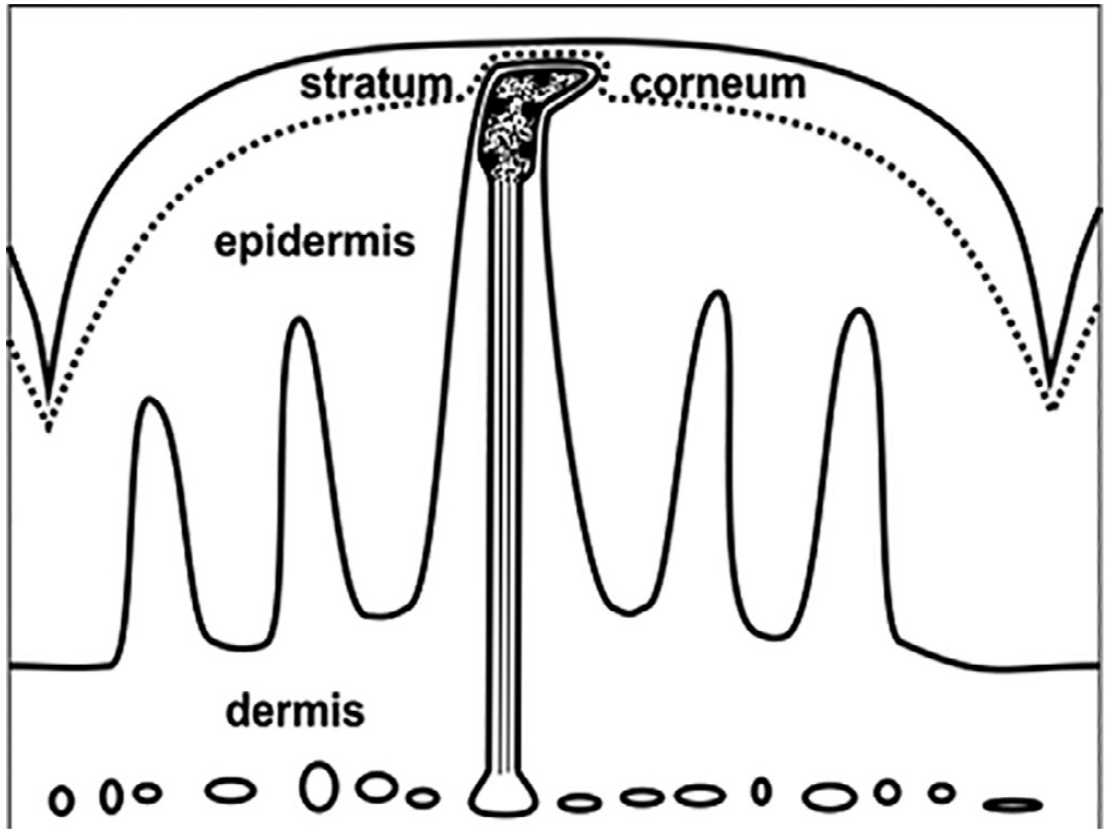


"Onion-like" structure

# New Somatosensory Organ in Dogs?





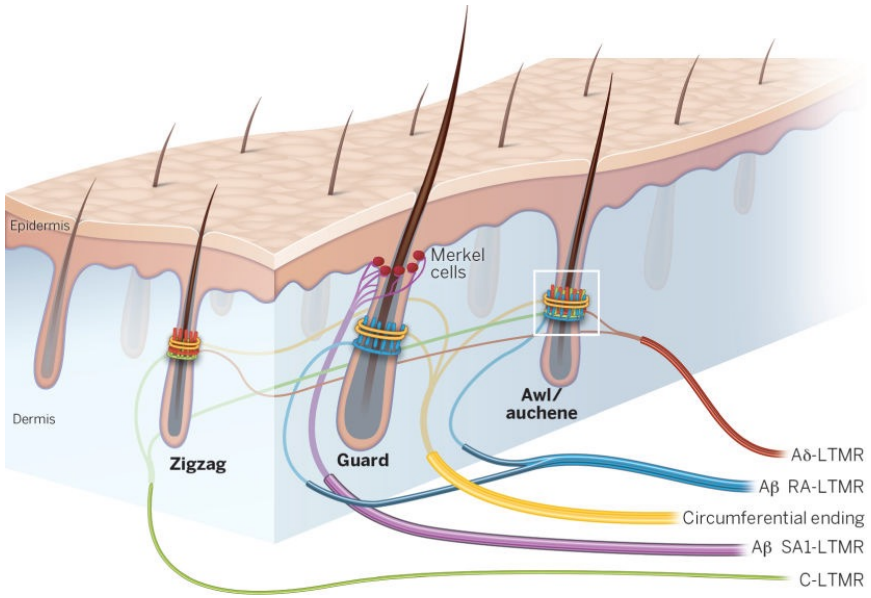



Nonencapsulated naked nerve bundles

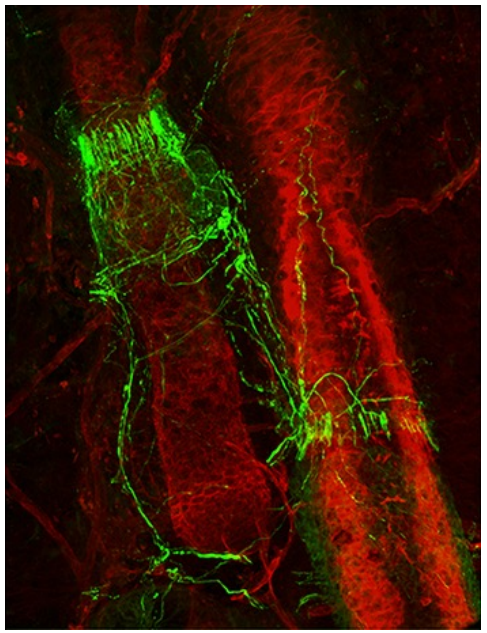
# Mechanoreceptors in Skin

## Hair follicle

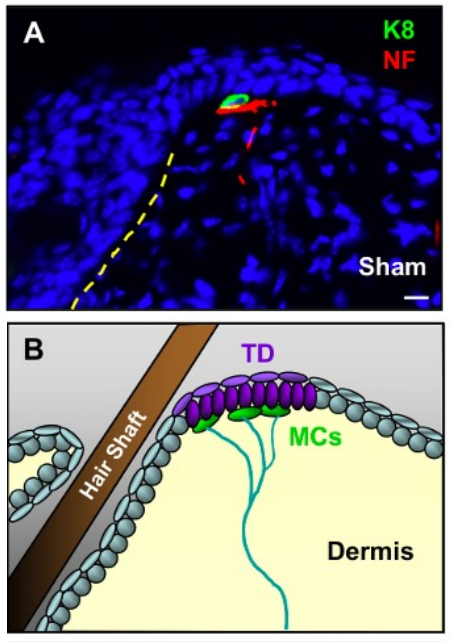
- *Light touch* (Low-frequency *vibration*)
- *All types* of sensory fibers




Zimmerman. 2014. *Science*

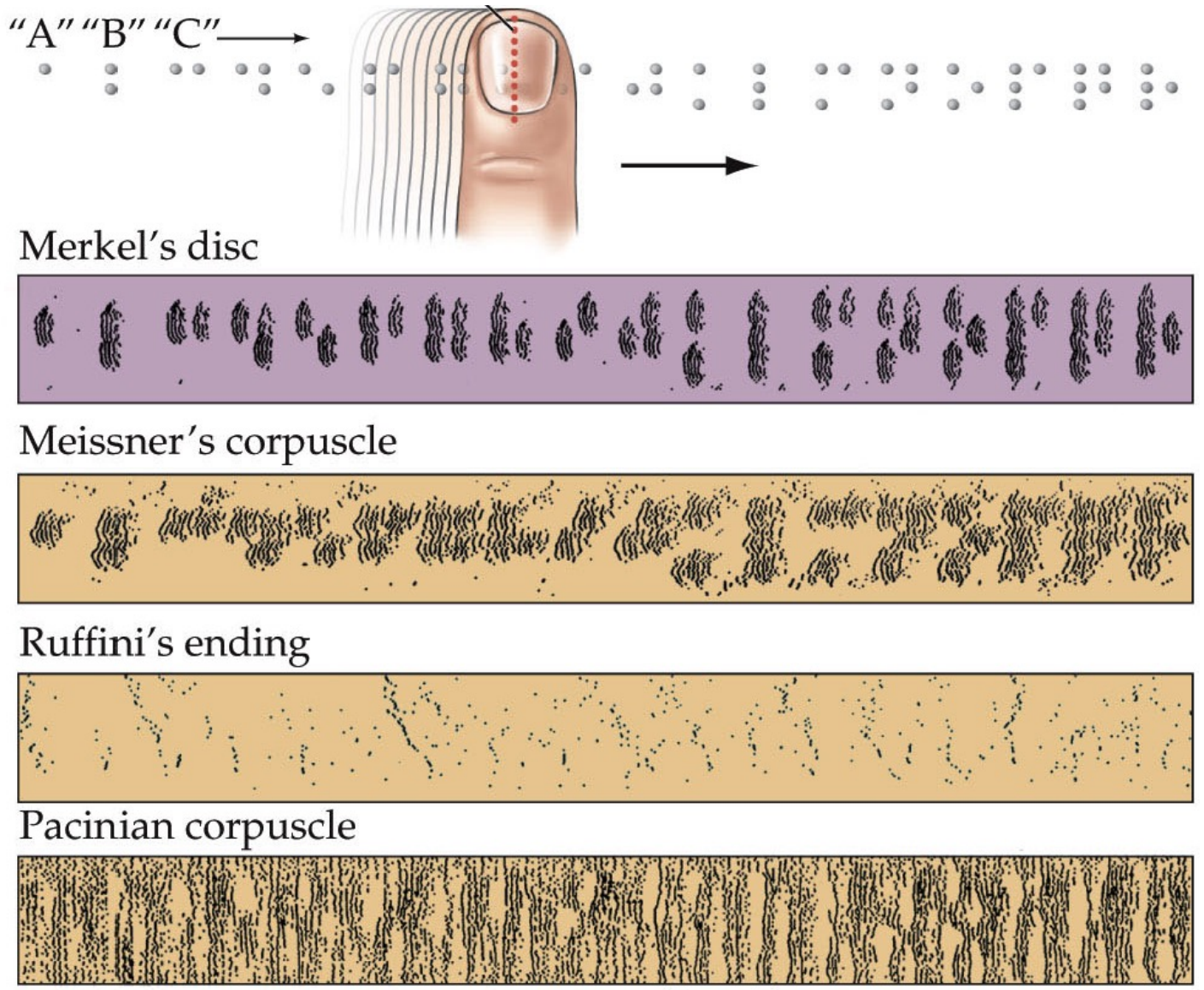


Nerves (PGP9.5)
Follicular keratinocytes (red)

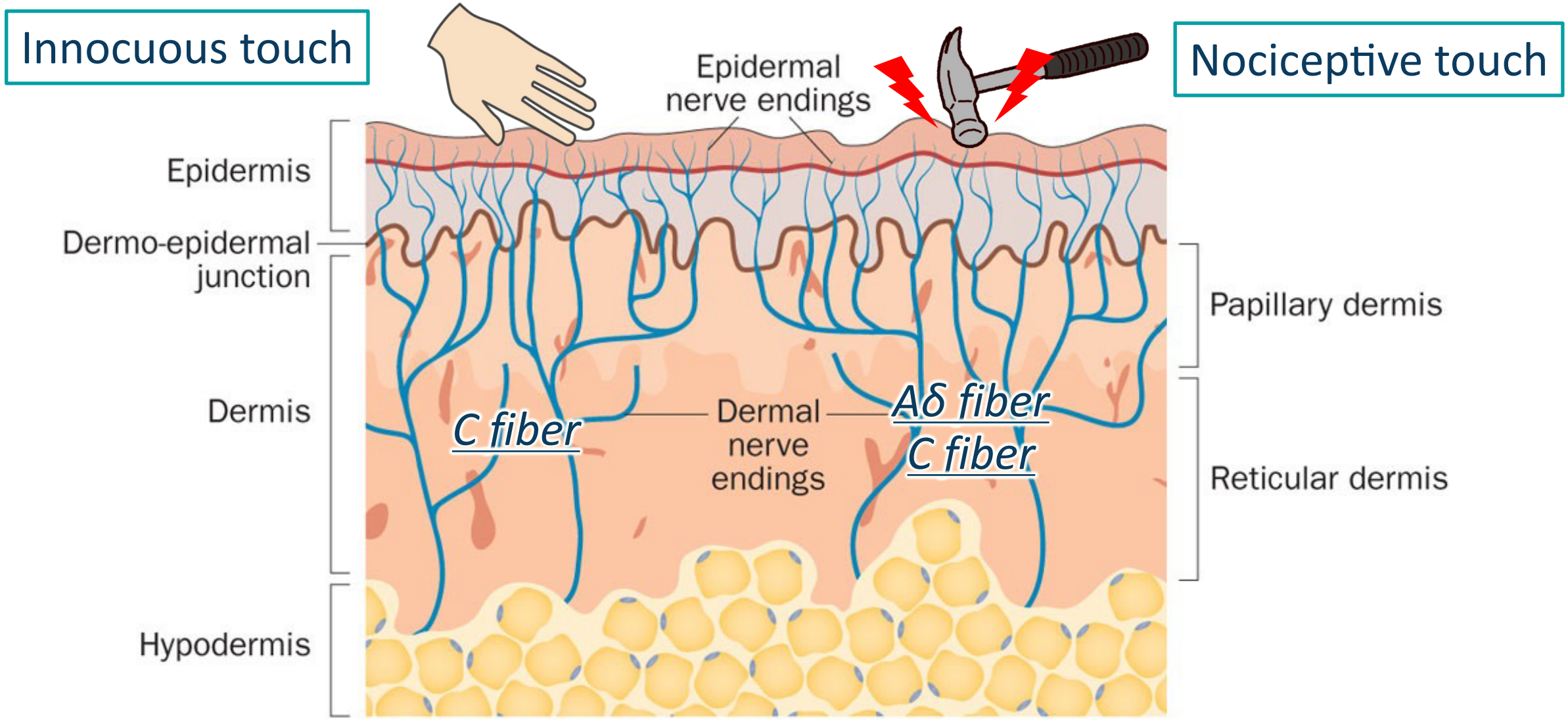



**Merkel cell touch dome** (K8)
Nerves (NF)

Each receptor sensors the same stimuli differently

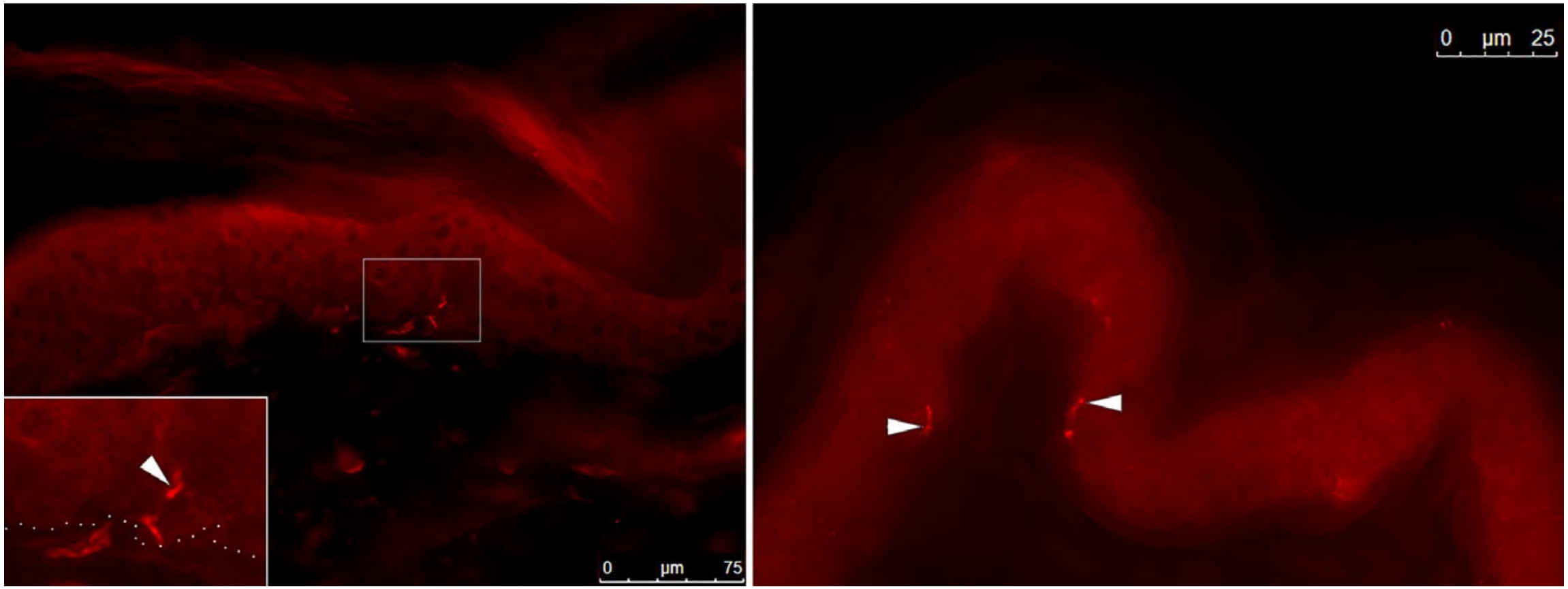


# Dermal and Epidermal Free Nerve Endings




Misery. 2014. *Nat Rev Neurol*

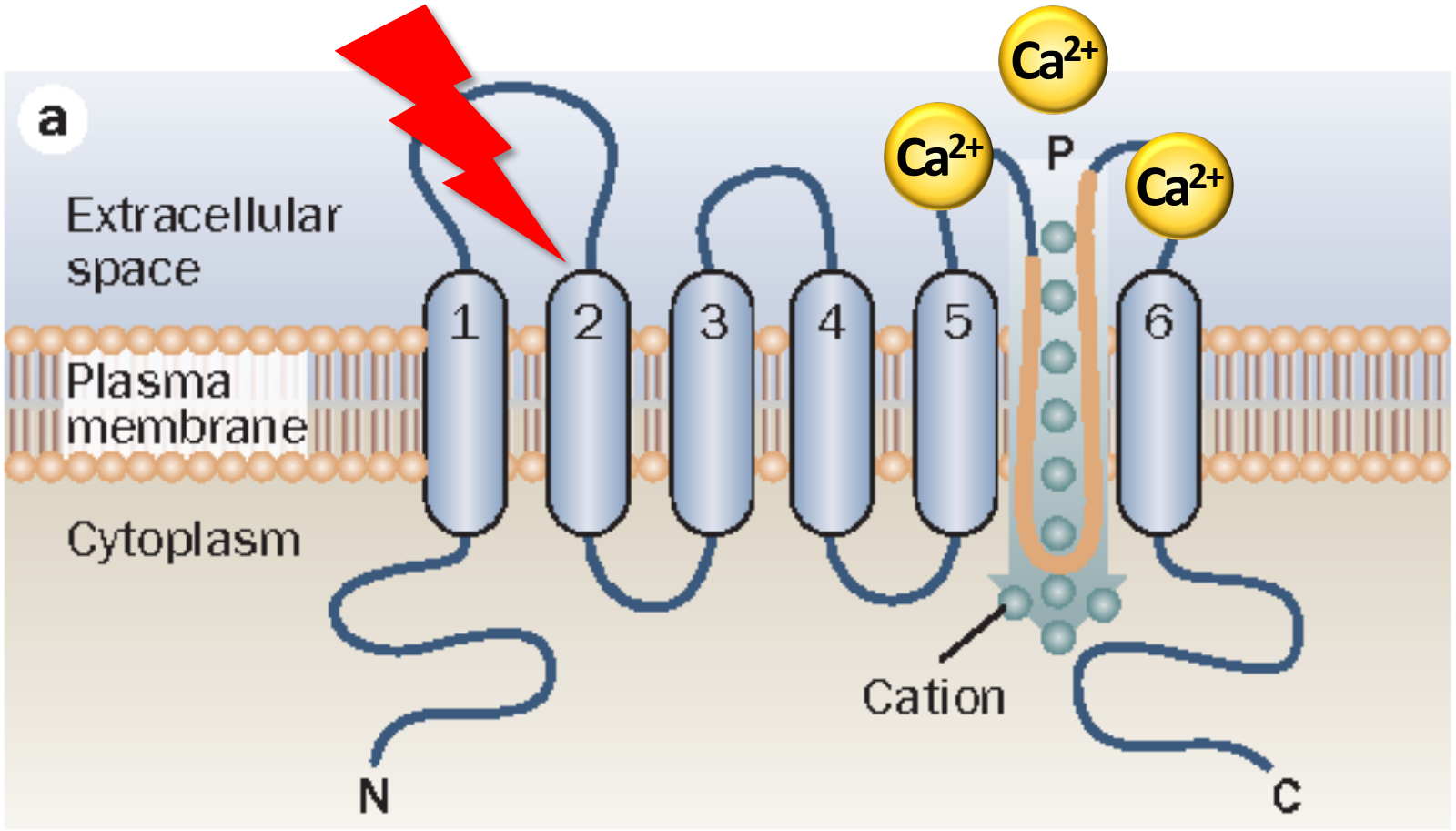
# Intraepidermal Nerve Endings

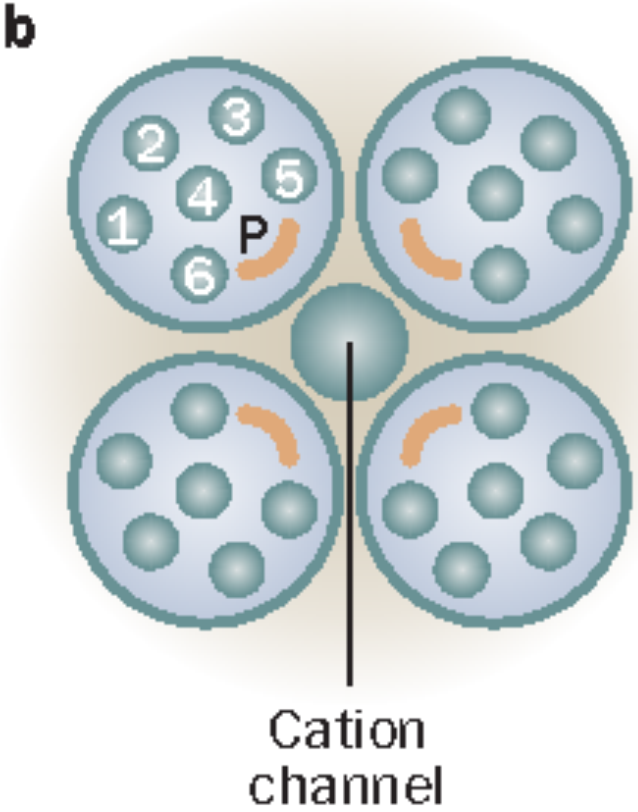



Canine skin – Interaepidermal nerve fibers (b3T)

Laprais. 2017. *Vet Dermatol*

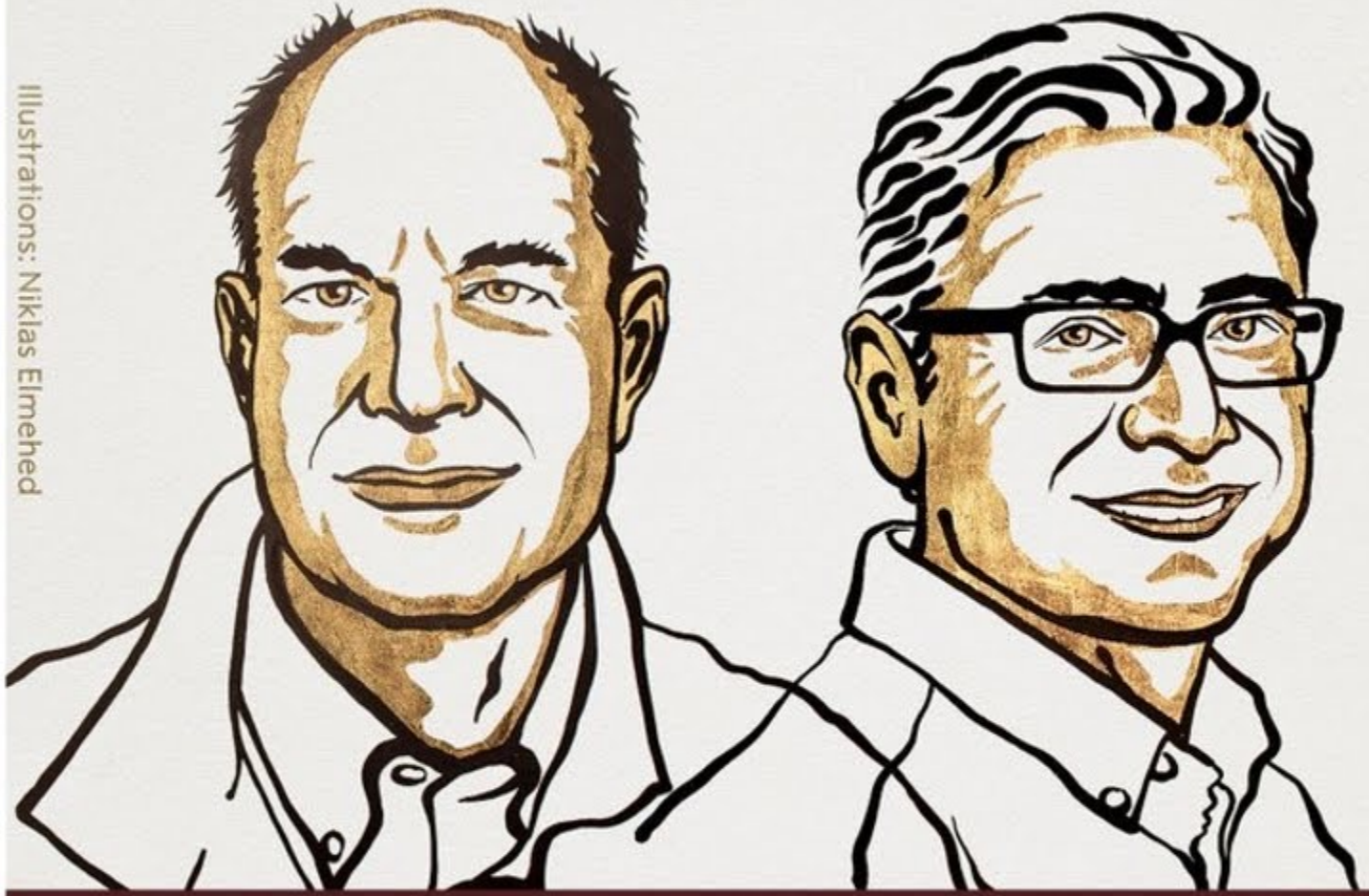
# Thermoreceptors – Transient Receptor Potential




→ Depolarization

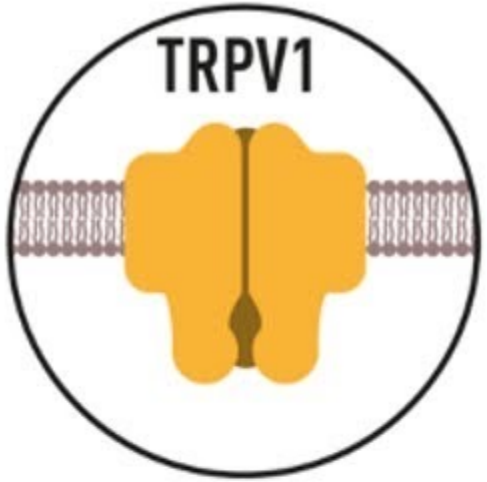
# THE NOBEL PRIZE IN PHYSIOLOGY OR MEDICINE 2021



Illustrations: Niklas Elmehed

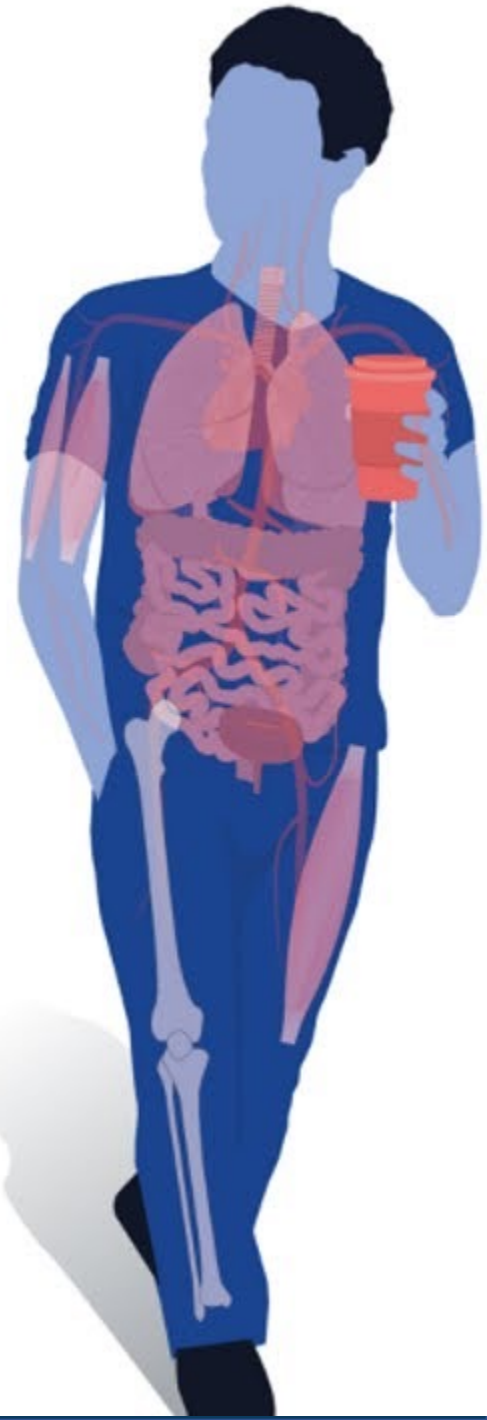
David Julius  Ardem Patapoutian

"for their discoveries of receptors for temperature and touch"

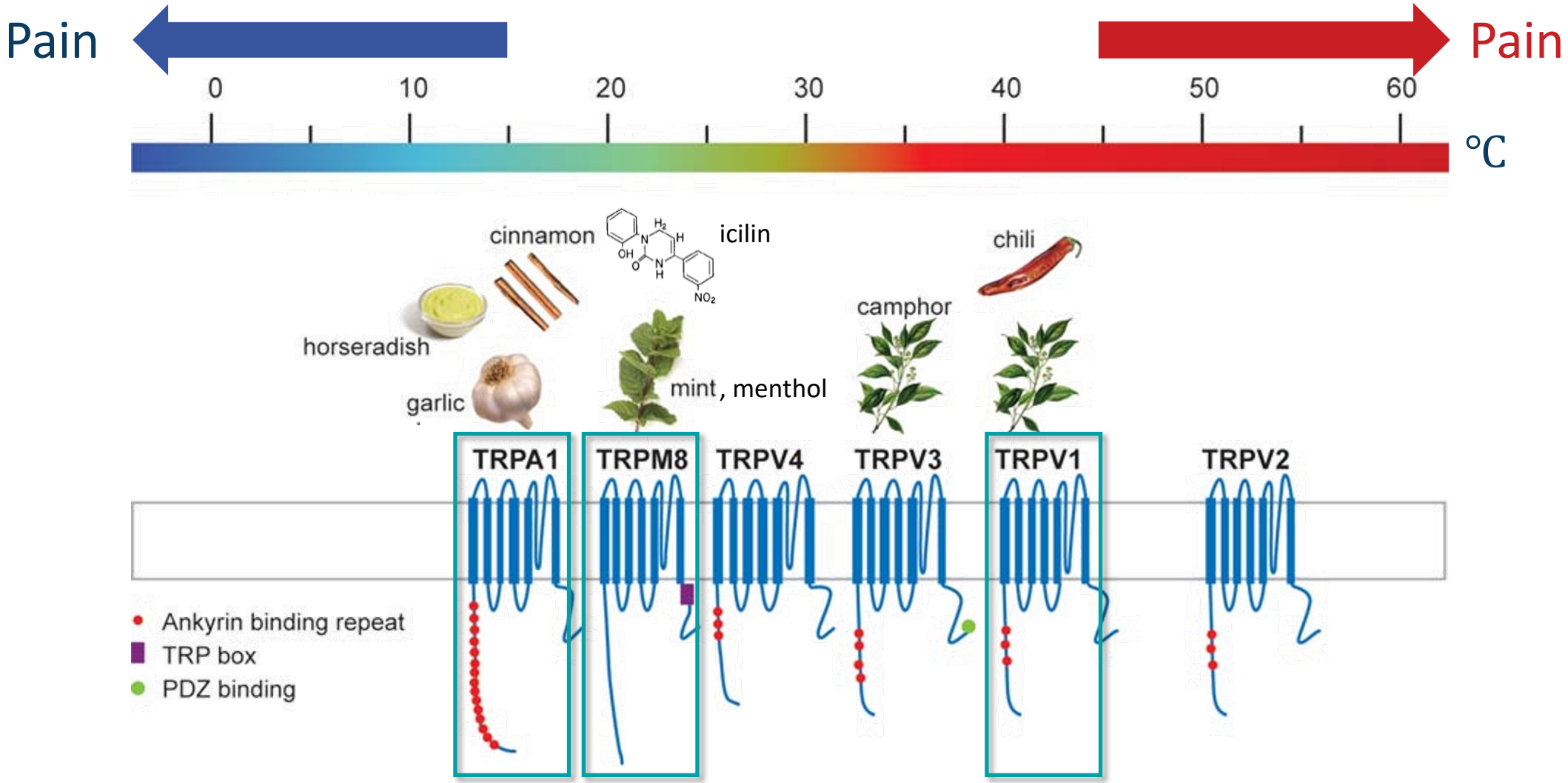



**Temperature**
**Heat pain**

Core body temperature
Inflammatory pain
Neuropathic pain
Visceral pain
Protective reflexes

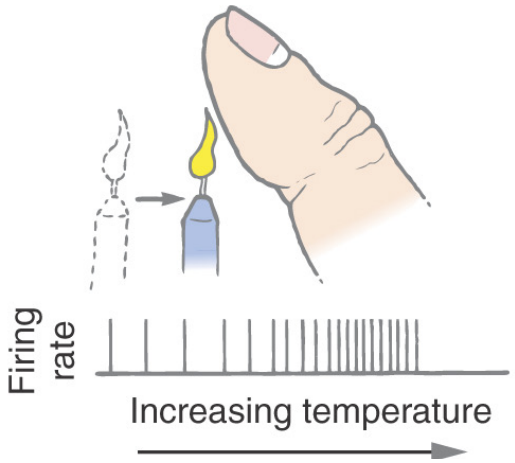


# Thermoreceptors – Transient Receptor Potential




Dhaka. 2006. *Annu. Rev Neurosci*

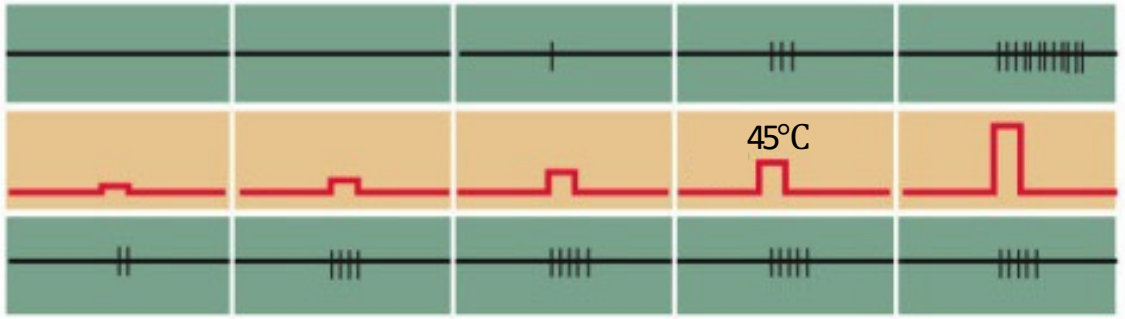
# Nociceptor (Pain) vs Thermoreceptor (Heat)

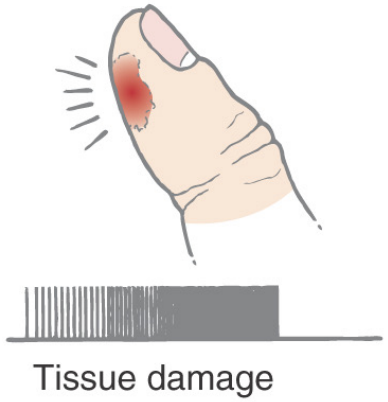



Nociceptor

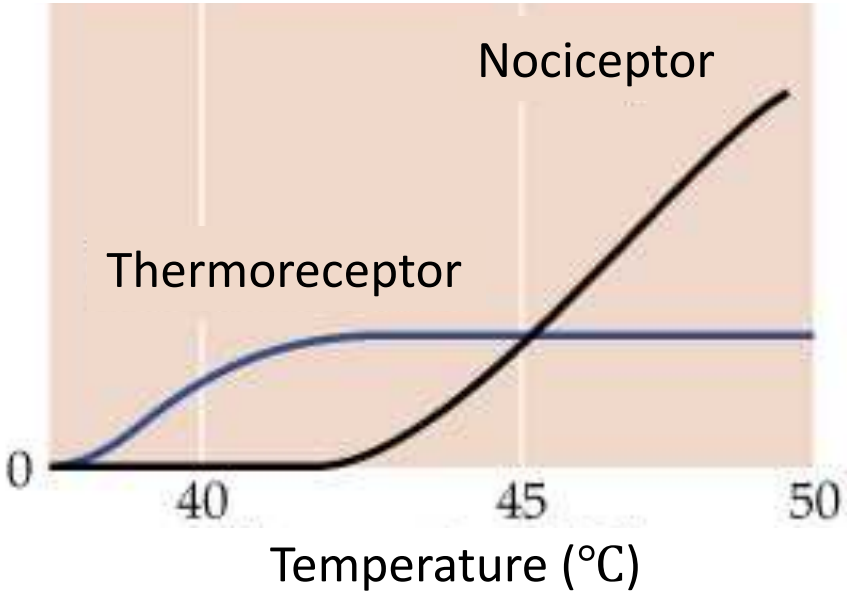
Stimulus

Thermoreceptor




Magnitude of afferent response



# Quiz!

**1. Which of the following mechanoreceptor has the smallest receptive?**

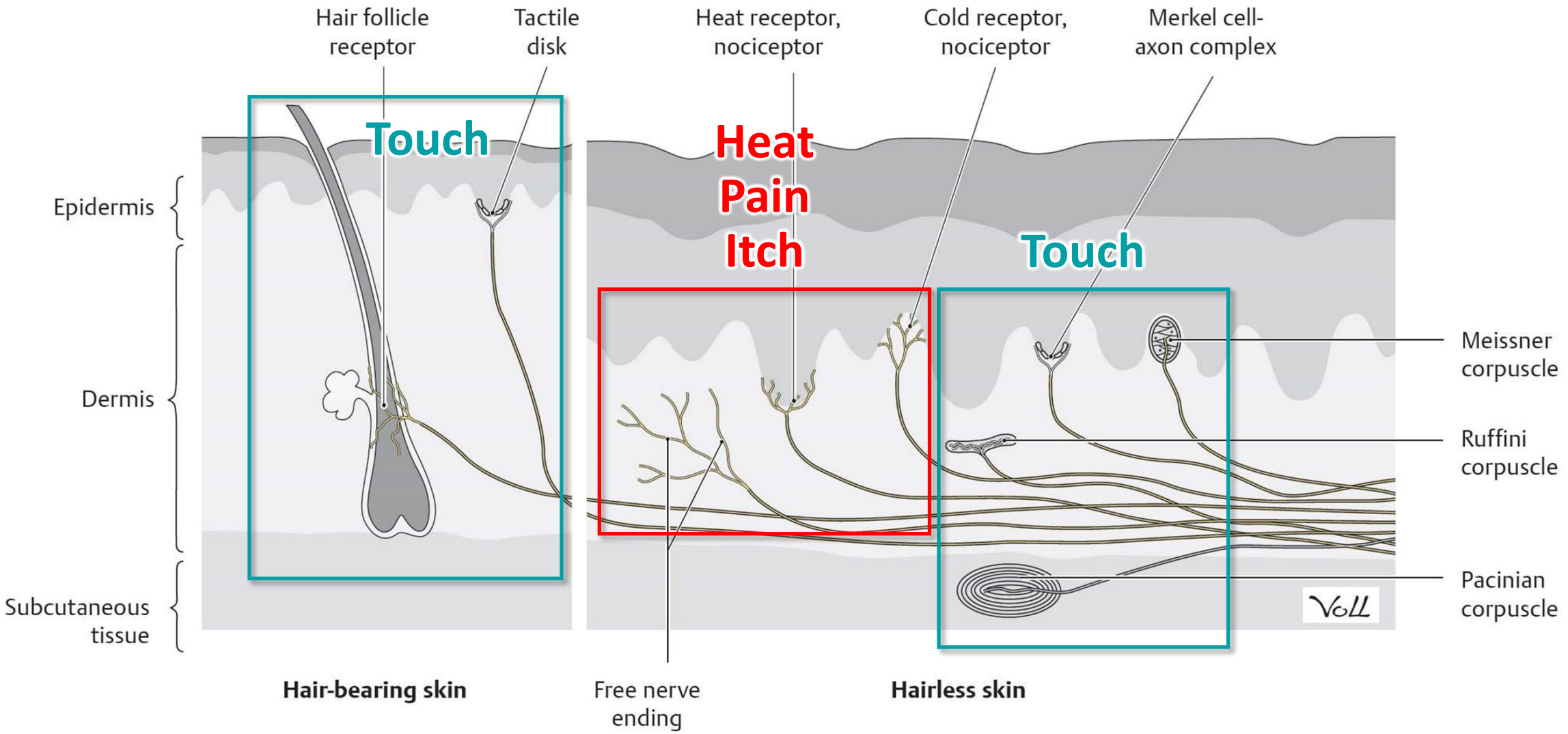
a. Merkel cell axon complex

b. Meissner corpuscle

c. Ruffini corpuscle

d. Pacinian corpuscle

# Summary – Cutaneous Sensory Receptors

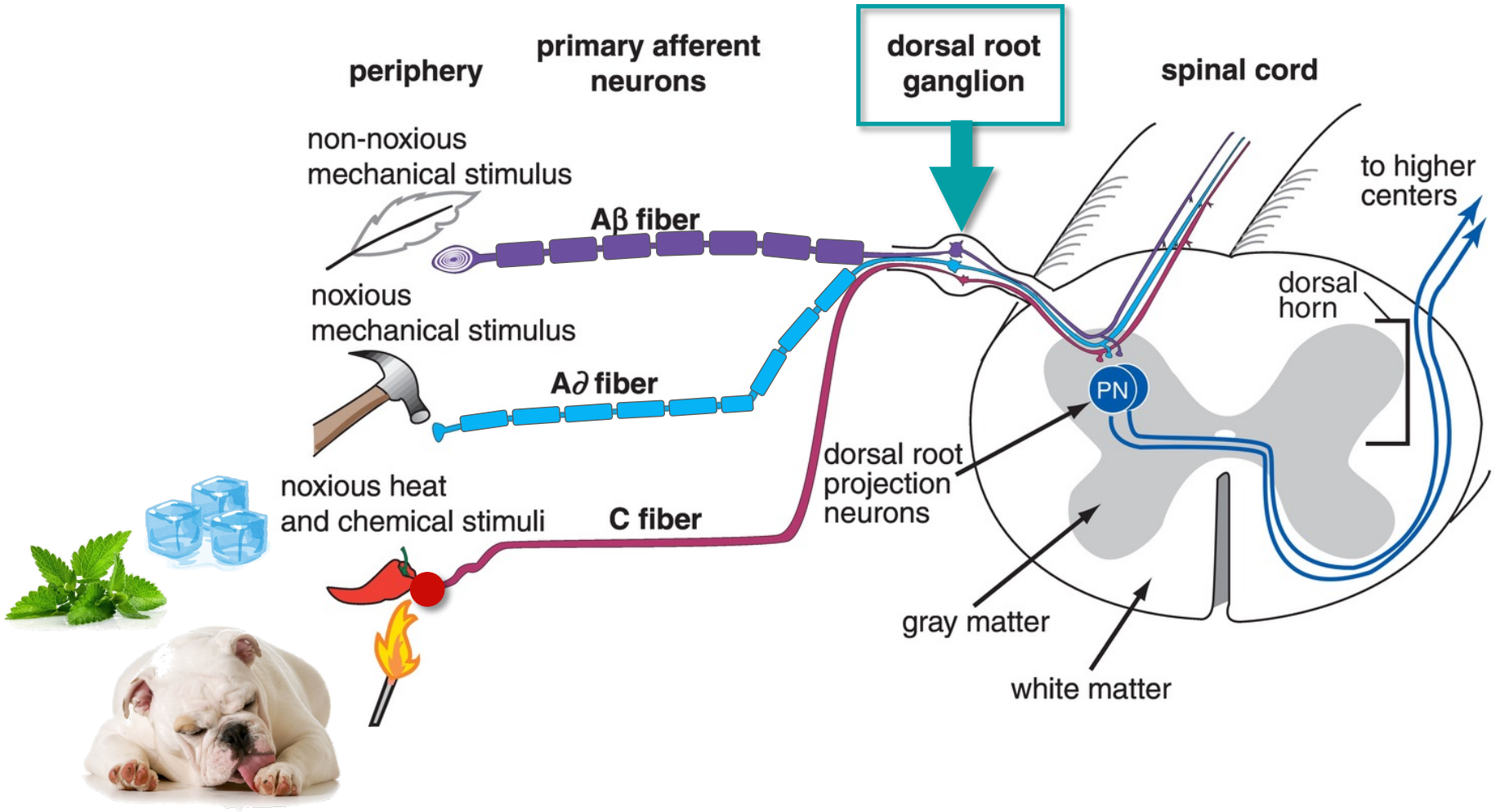


# Classicization of Cutaneous Sensory Nerve Fibers

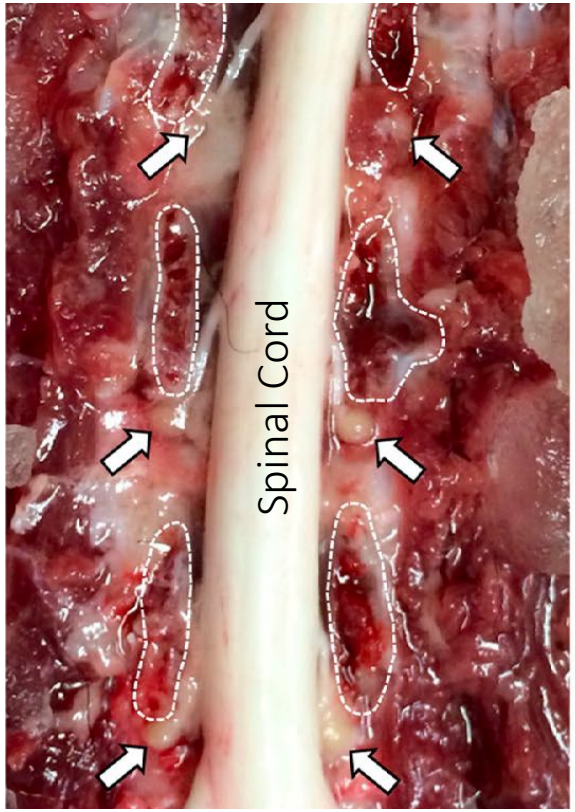
| Types of nerve fibers | | Axon diameter | Conduction velocity | Receptor types | Sensory function |
|---|---|---|---|---|---|
| **Aβ/II** |  | Medium | Medium | Merkel cells, Meissner's corpuscles, Ruffini endings, Pacinian corpuscles, hair follicles | Touch, pressure |
| **Aδ/III** |  | Small | Medium | Hair follicles, free nerve endings | Fast pain, temperature |
| **C/IV** |  | Smallest | Slow | Hair follicles, free nerve endings | Slow pain, temperature, itch |

Glatte. 2019. *Front Neurol.*

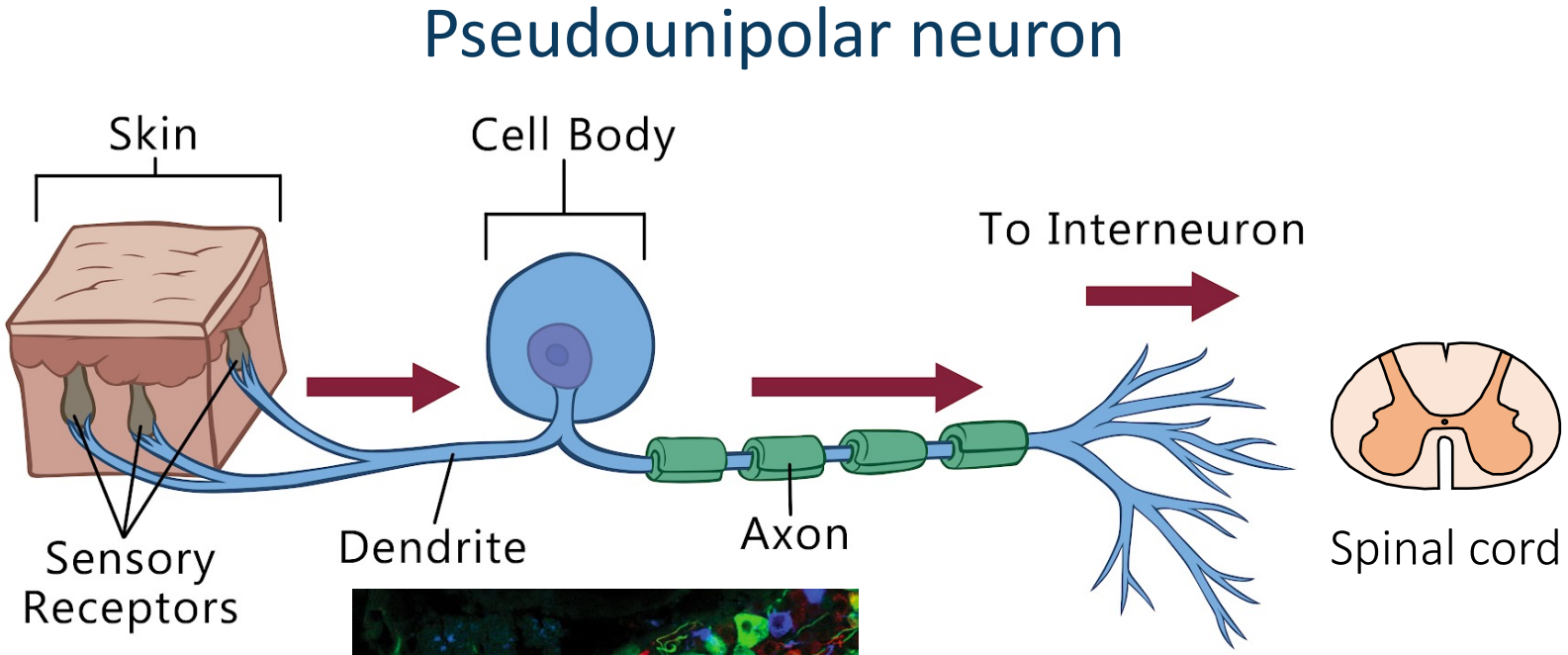
# Classicization of Cutaneous Sensory Nerve Fibers

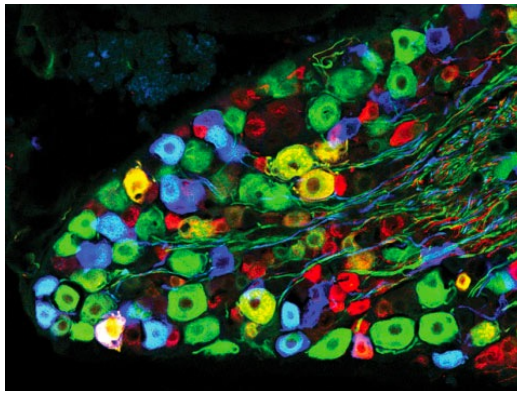


# Dorsal Root Ganglion



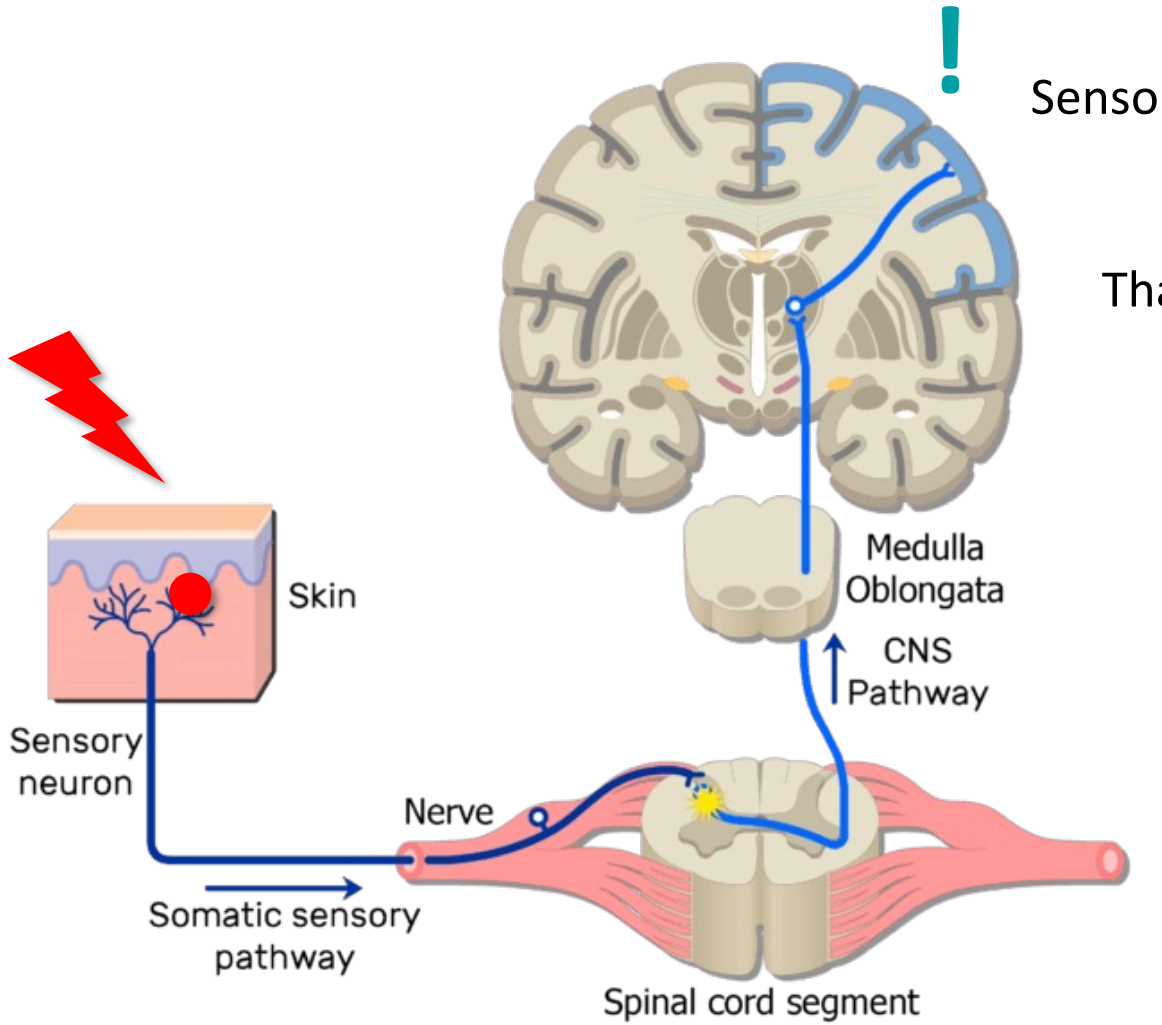

Ganchiogco 2019. *Brain Behav*



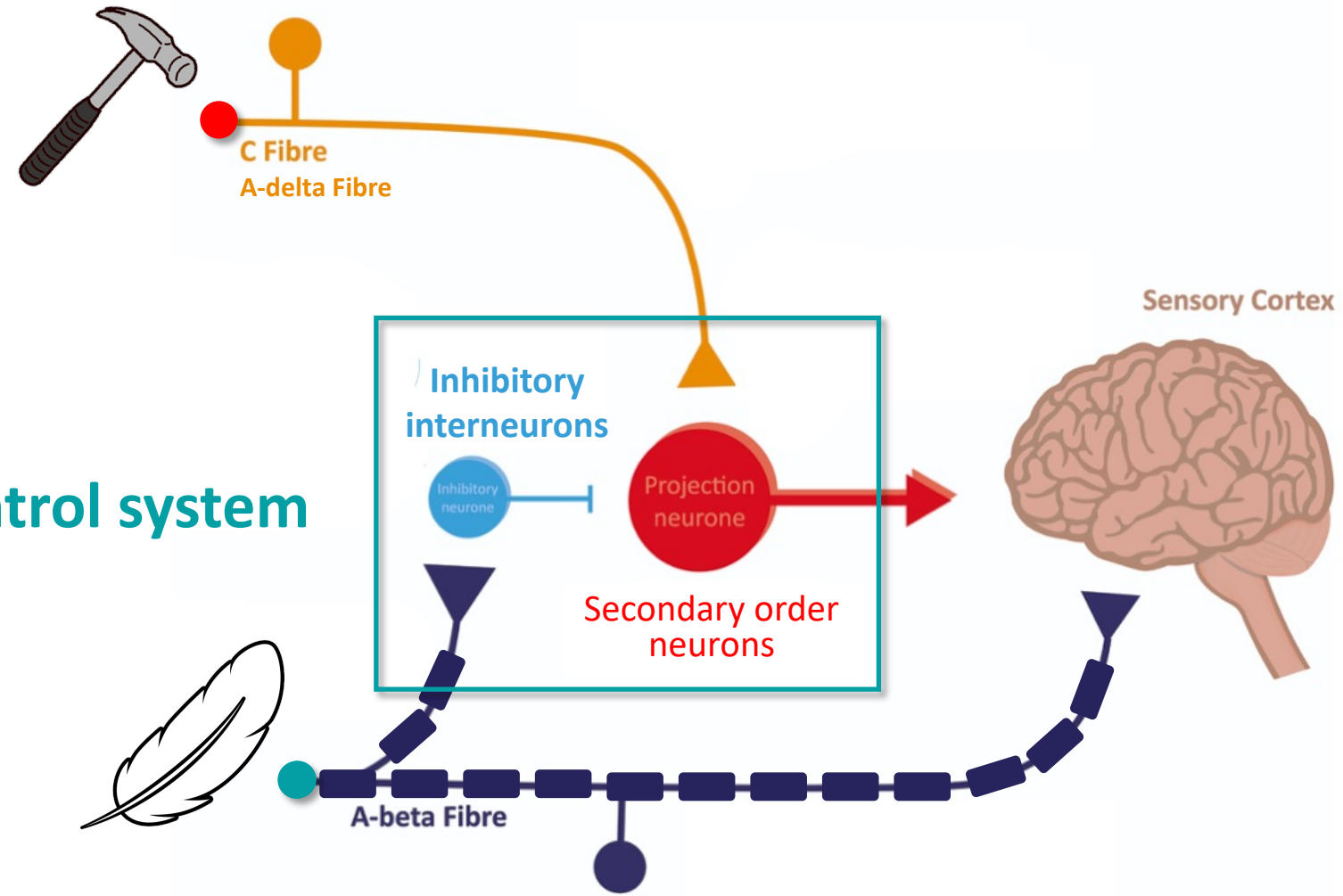
LaTasha. 2020. *Toxicol Pathol*

# Sensation from Skin to Brain



# Gate Control Theory

## Gate control system



# Quiz!

**2. Which description correctly characterize C nerve fivers?**

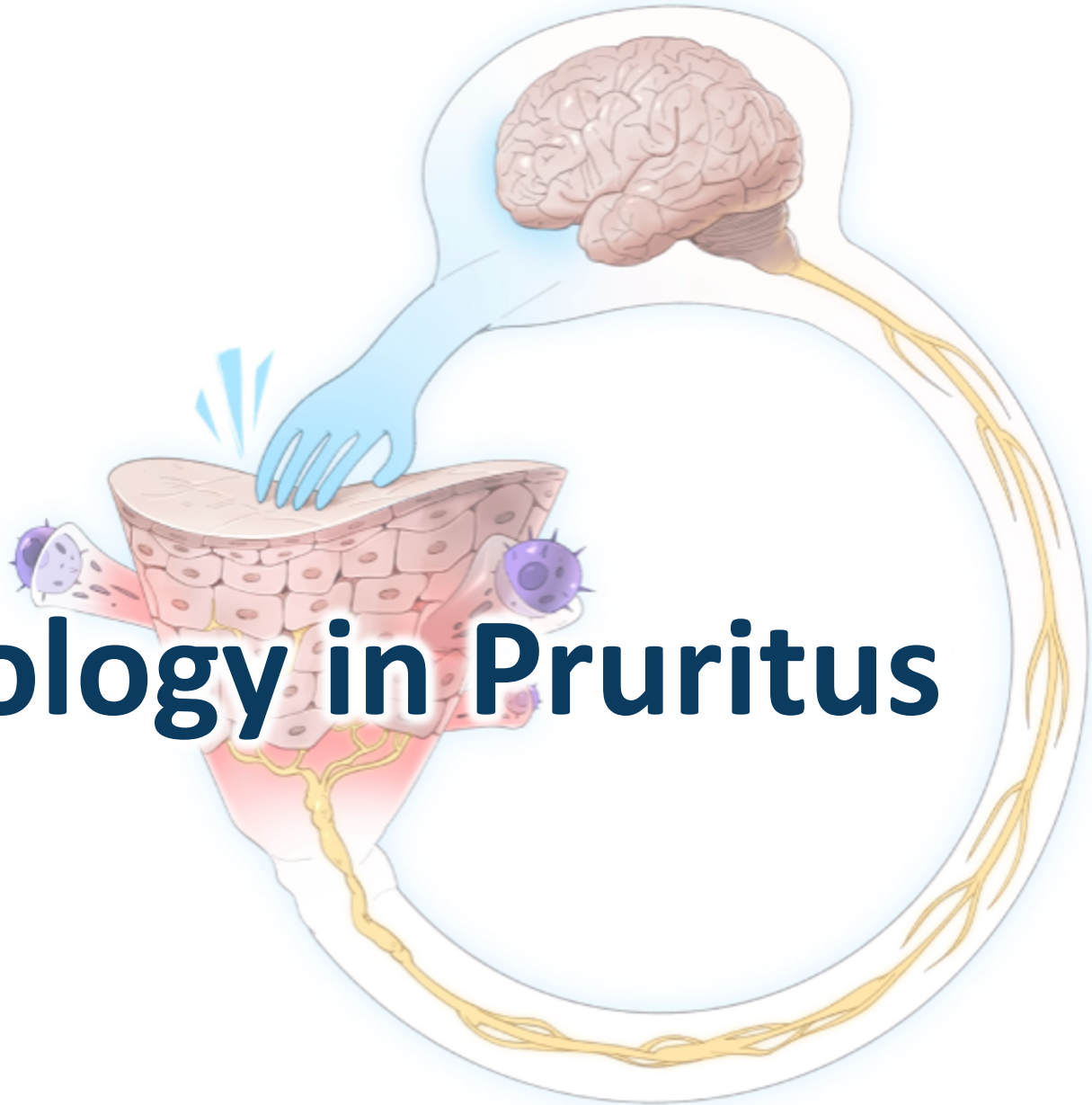
a. Myelinated, large diameter, fast conduction velocity

b. Myelinated, small diameter, slow conduction velocity

c. Unmyelinated, small diameter, fast conduction velocity

d. Unmyelinated, small diameter, slow conduction velocity

# 2. Pathology in Pruritus



# Itch

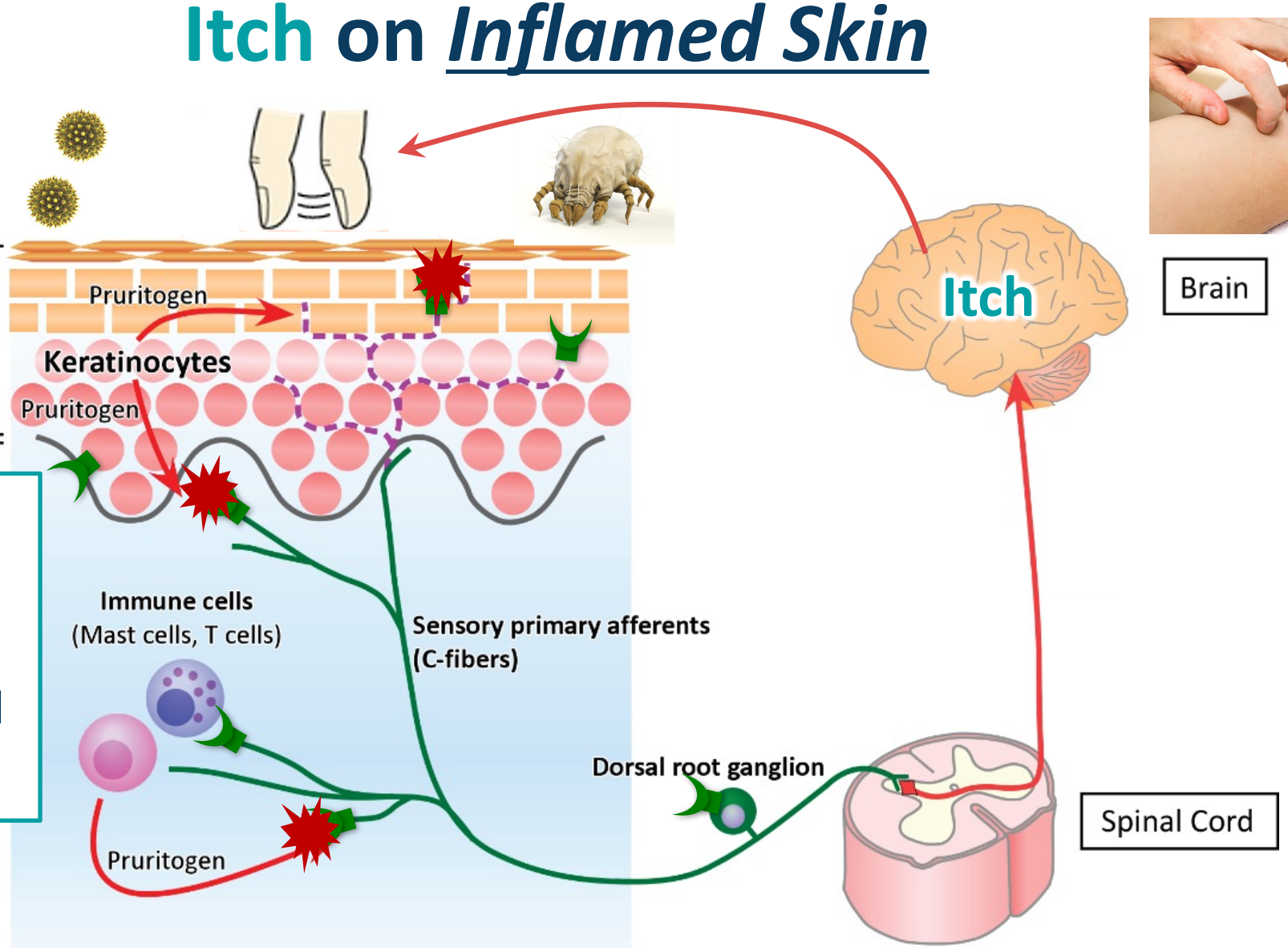
An unpleasant sensation which causes an intense desire to scratch

1. **Itch** on primary, *inflamed skin*
2. **Itch** on primary, *non-inflamed skin*
3. Secondary scratch lesion

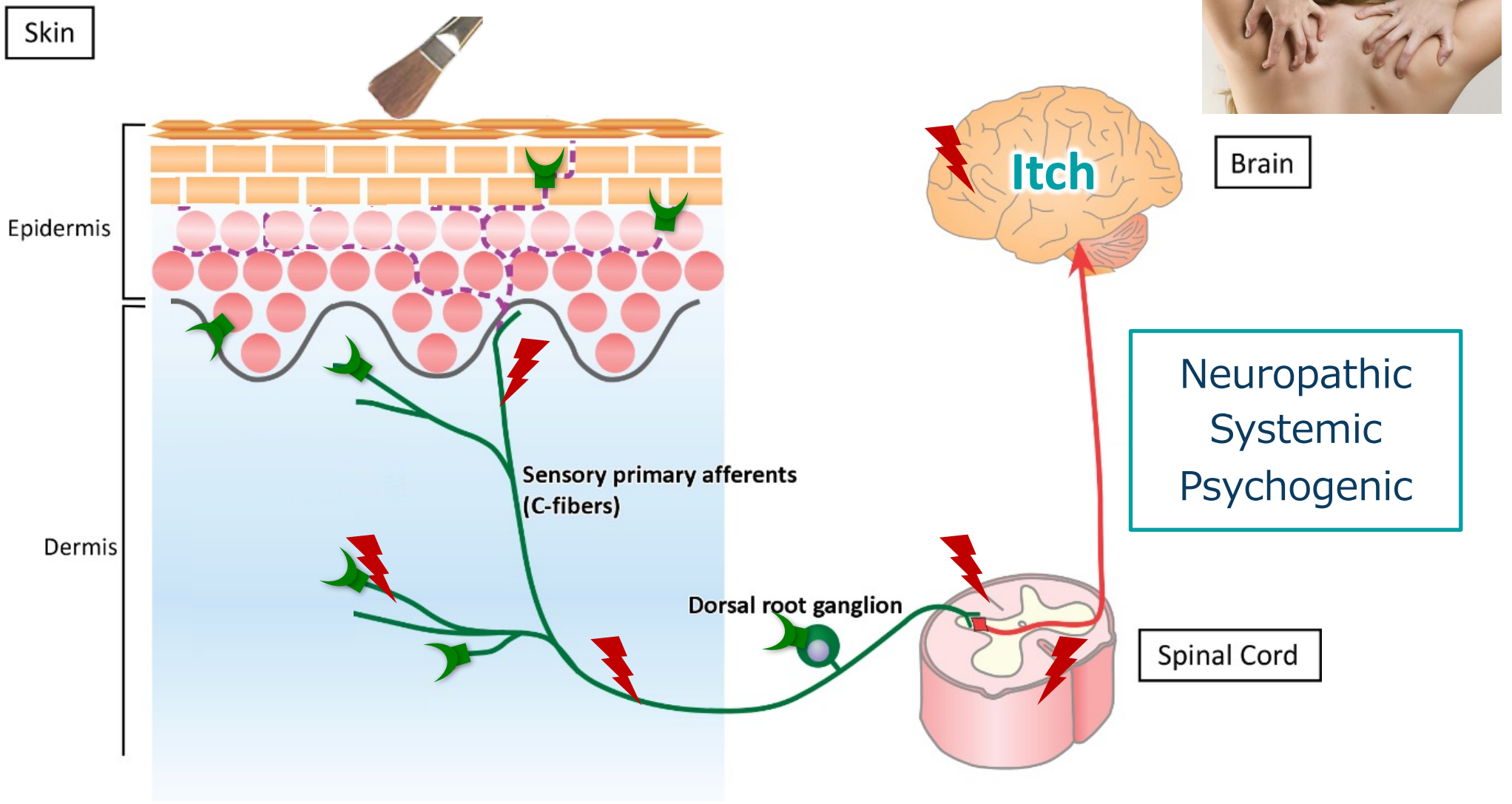
# Itch on *Inflamed Skin*

Secondary scratch lesion

Infections
Ectoparasites
Allergies
Immune-mediated
Skin cancers




# Itch on *Non-Inflamed Skin*



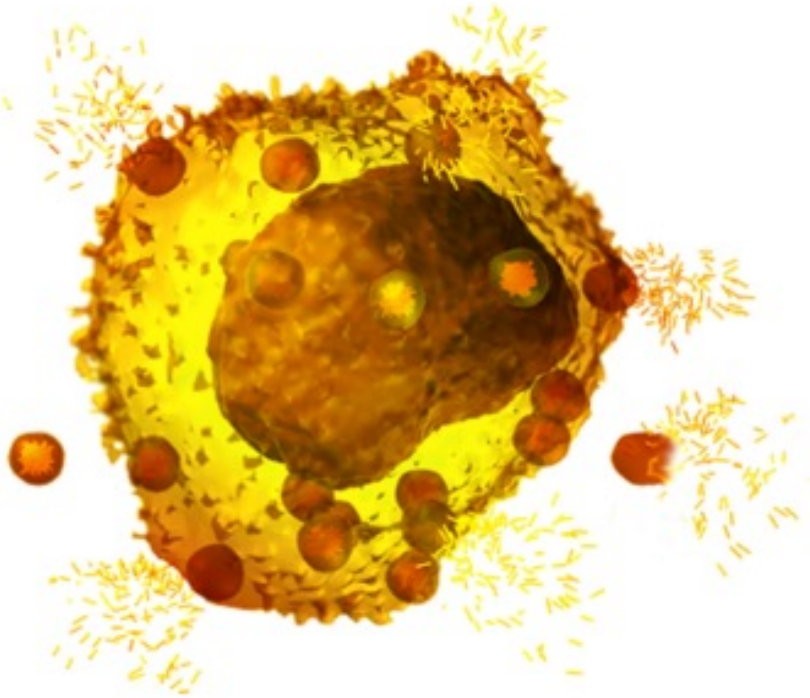

# Pruritogen

Any substance/mediators that cause pruritus

1. *Amines* – histamine, serotonin
2. *Neuropeptides* – substance P, NGF
3. *Protease* – KLKs, tryptase/chymase, exogenous proteases (HDM, Staphylococcus *sp*.)
4. *Cytokines* – TSLP, IL-2, IL-4, IL-13, IL-31, IL-33

# Histaminergic Itch

Histamine



Mast cells, basophils

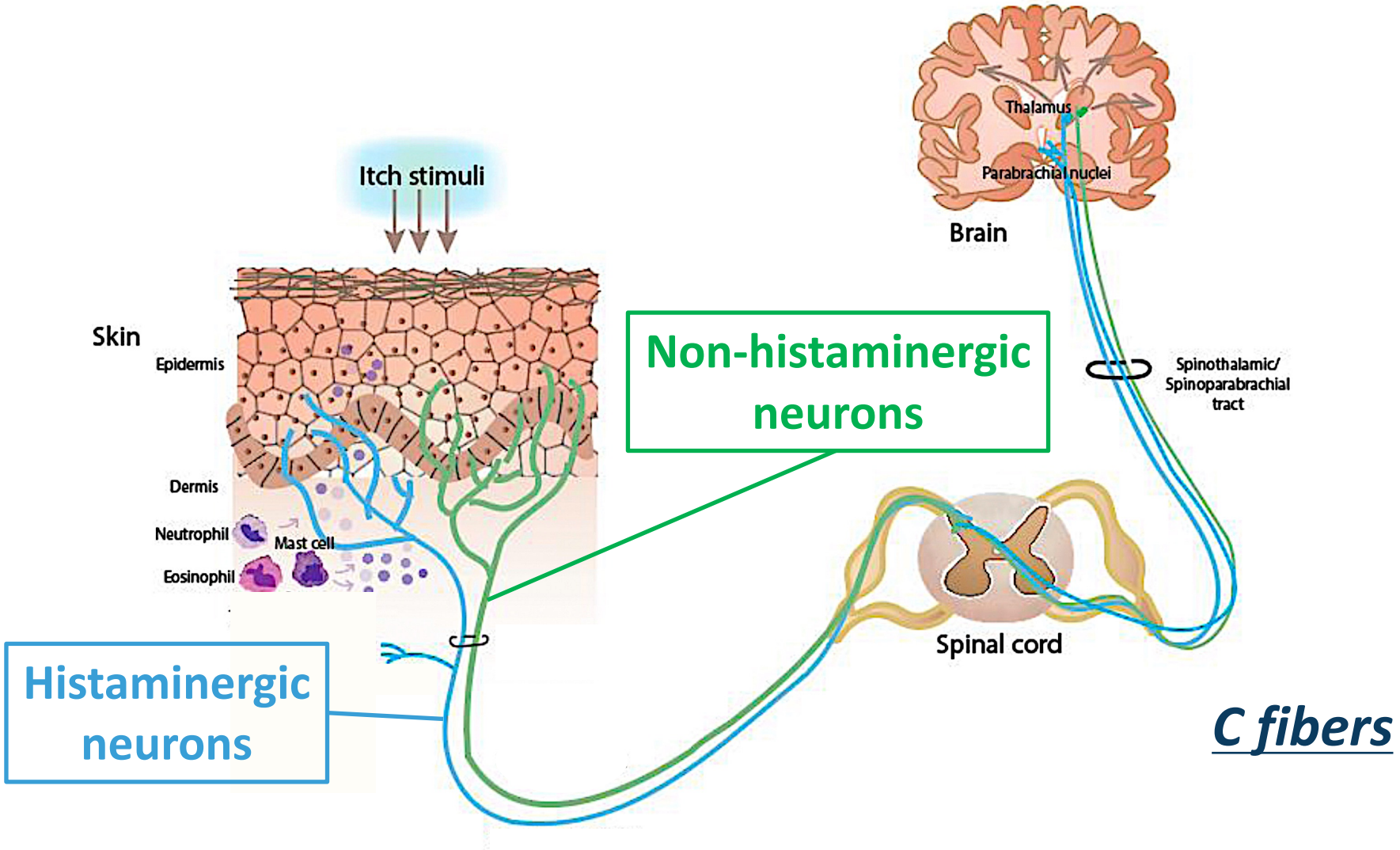
vs

# Non-histaminergic Itch

Mucunain

Cowhage (Velvet beans)

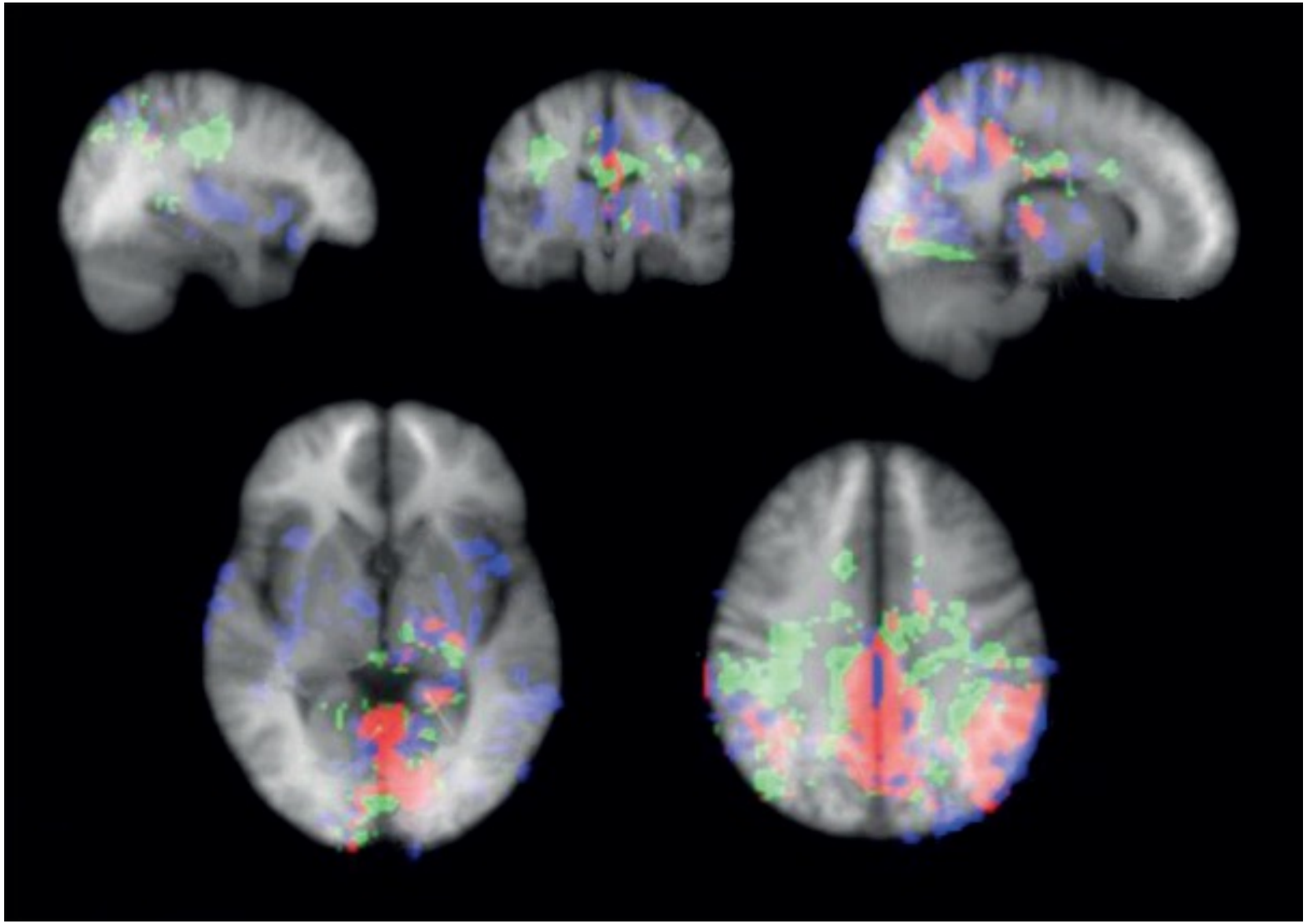
# Histaminergic vs Non-histaminergic Itch Pathways



# Histaminergic vs Non-histaminergic Itch Pathways

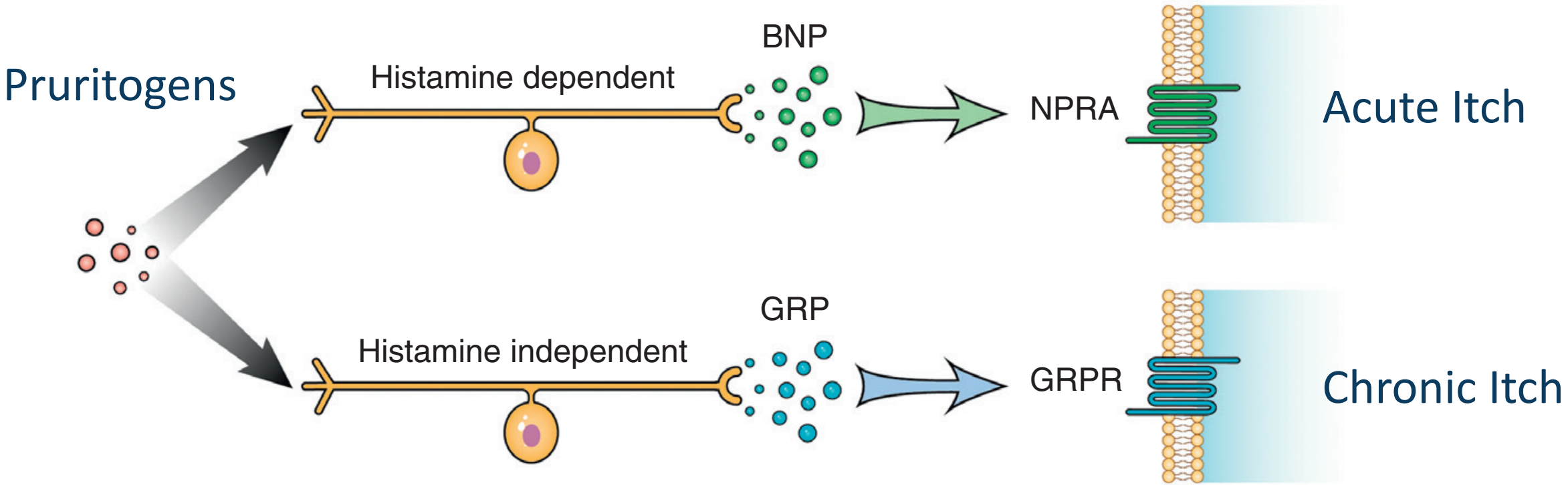
*Brain activation map*

- Histamine
- Cowhage (non-histaminergic)
- Co-activation



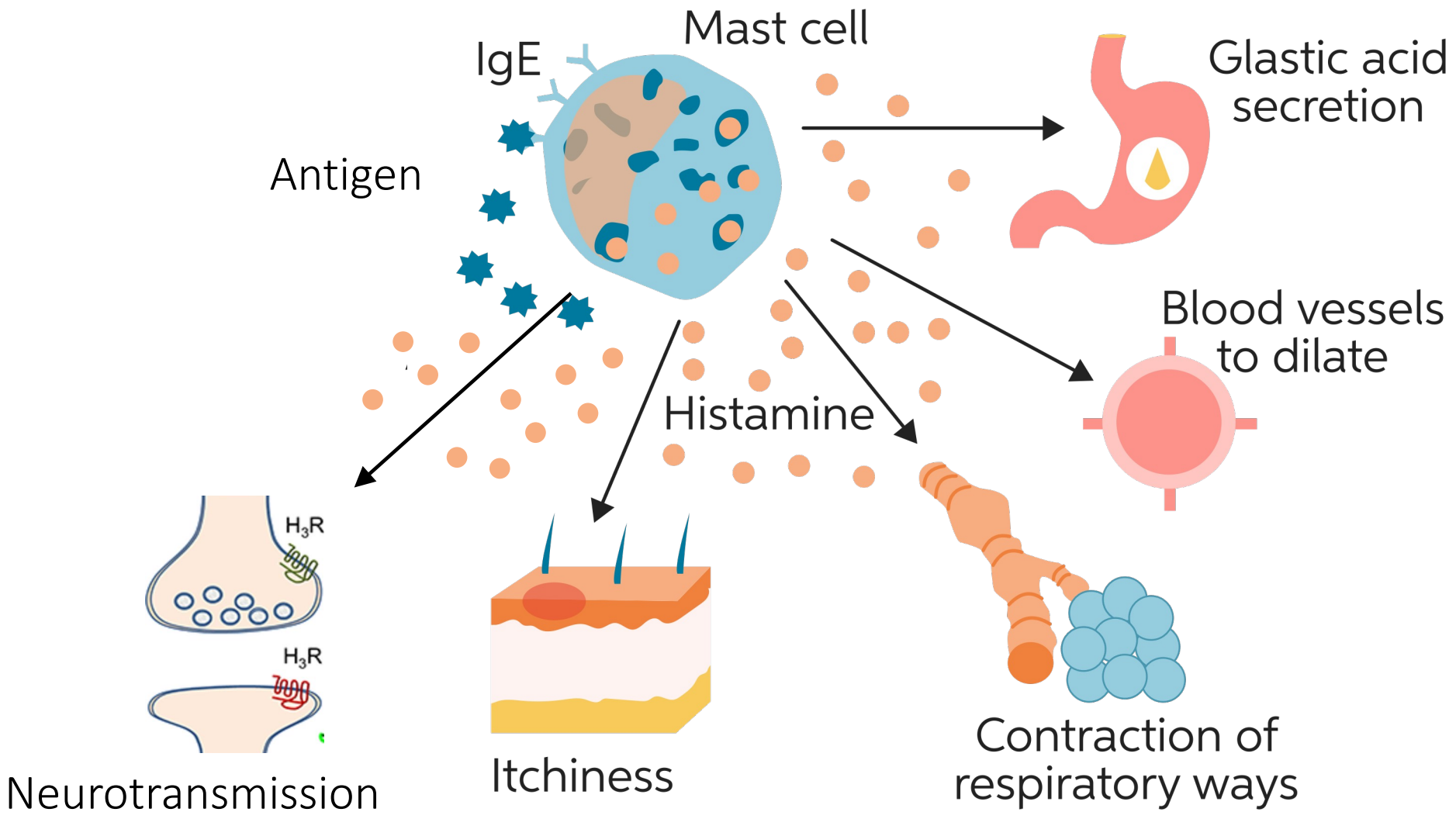
Papoiu. 2012. *NeuroImage*

# Acute vs Chronic Itch




Liu. 2020. *J Invest Dermatol*

# Amines – Histamine



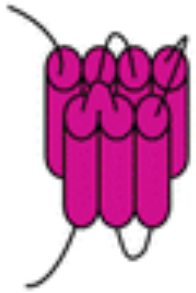
# Histamine Receptors

**$H_1$ Receptor**

Acute allergic reactions
Sleep disorder

**$H_2$ Receptor**

Gastric acid secretion



**$H_3$ Receptor**

Neurotransmitter modulation

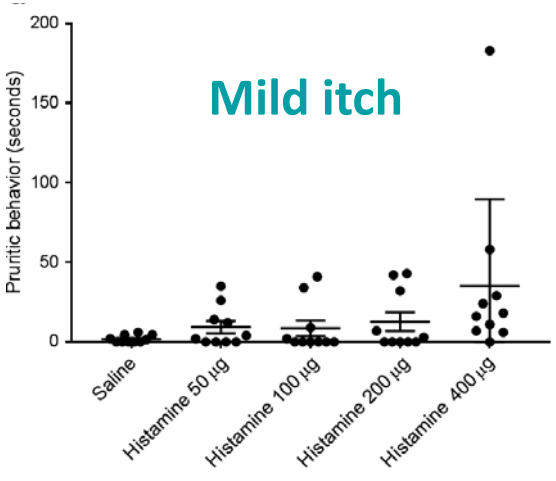
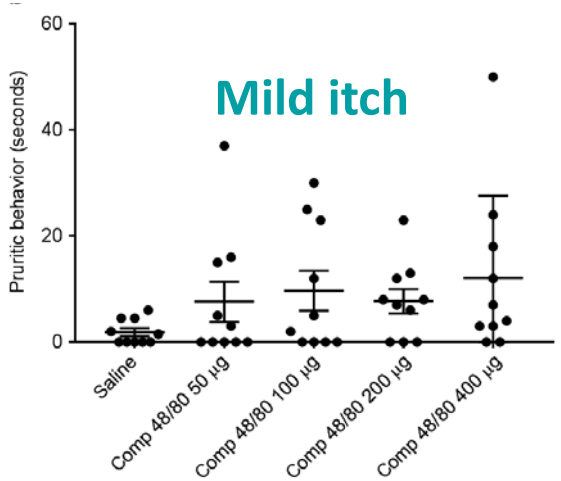
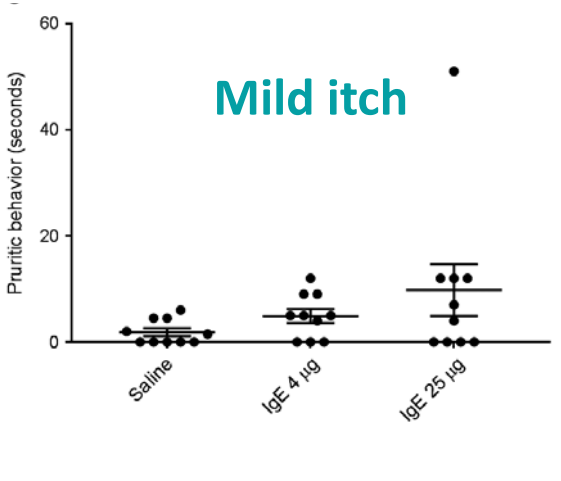
**$H_4$ Receptor**

Immunomodulation

**Itch**

**Itch**

# Does Histamine Induce Pruritus in Dogs?

| | Histamine | Comp 48/80 | Anti-canine-IgE |
|---|---|---|---|
| Wheal & Flare |  |  |  |
| Pruritus |  |  |  |

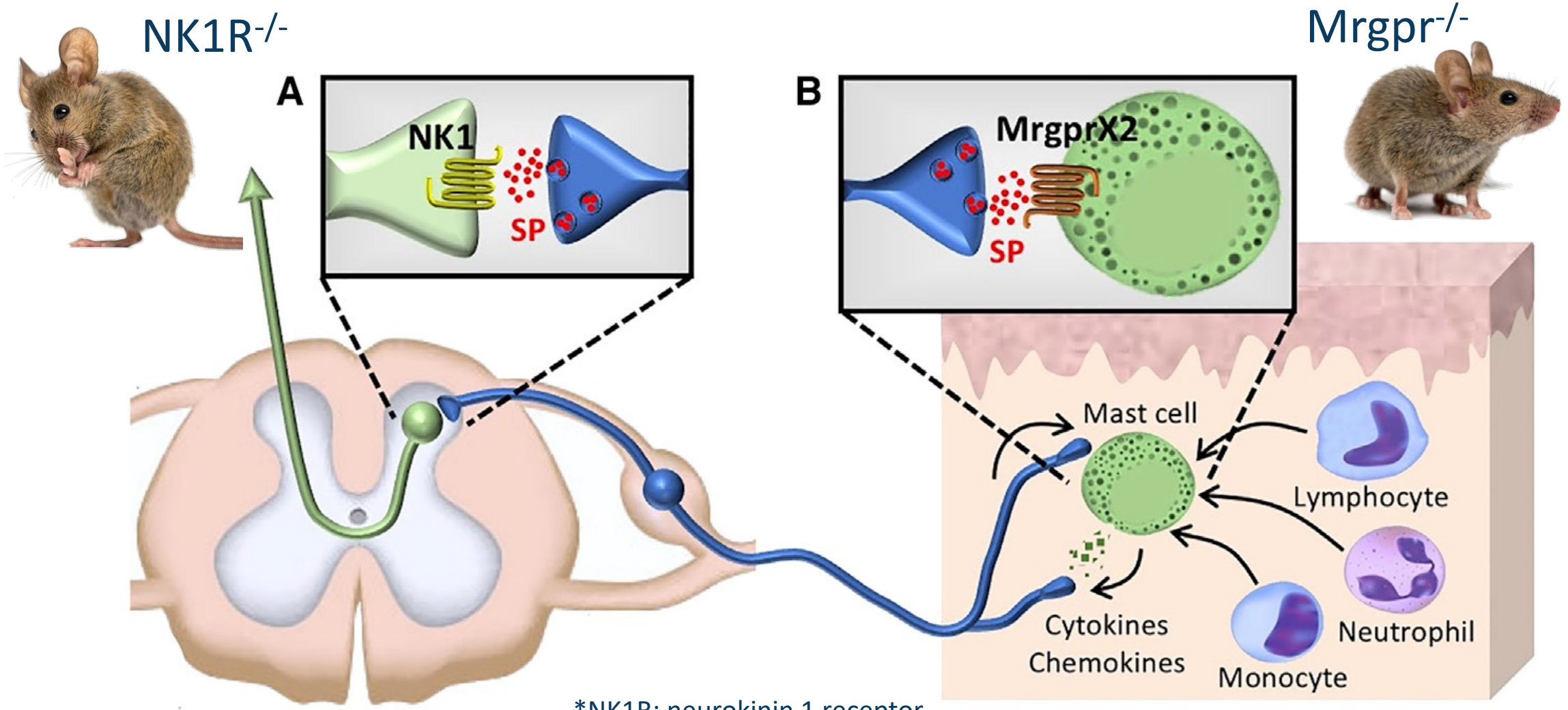






Banovic. 2019. *Vet Dermatol*

# Neuropeptides – Substance P




*NK1R: neurokinin 1 receptor
*Mrgpr: mas-related G protein-coupled receptors

# Does Substance P Induce Pruritus in Dogs?

## *Wheal & Erythema*

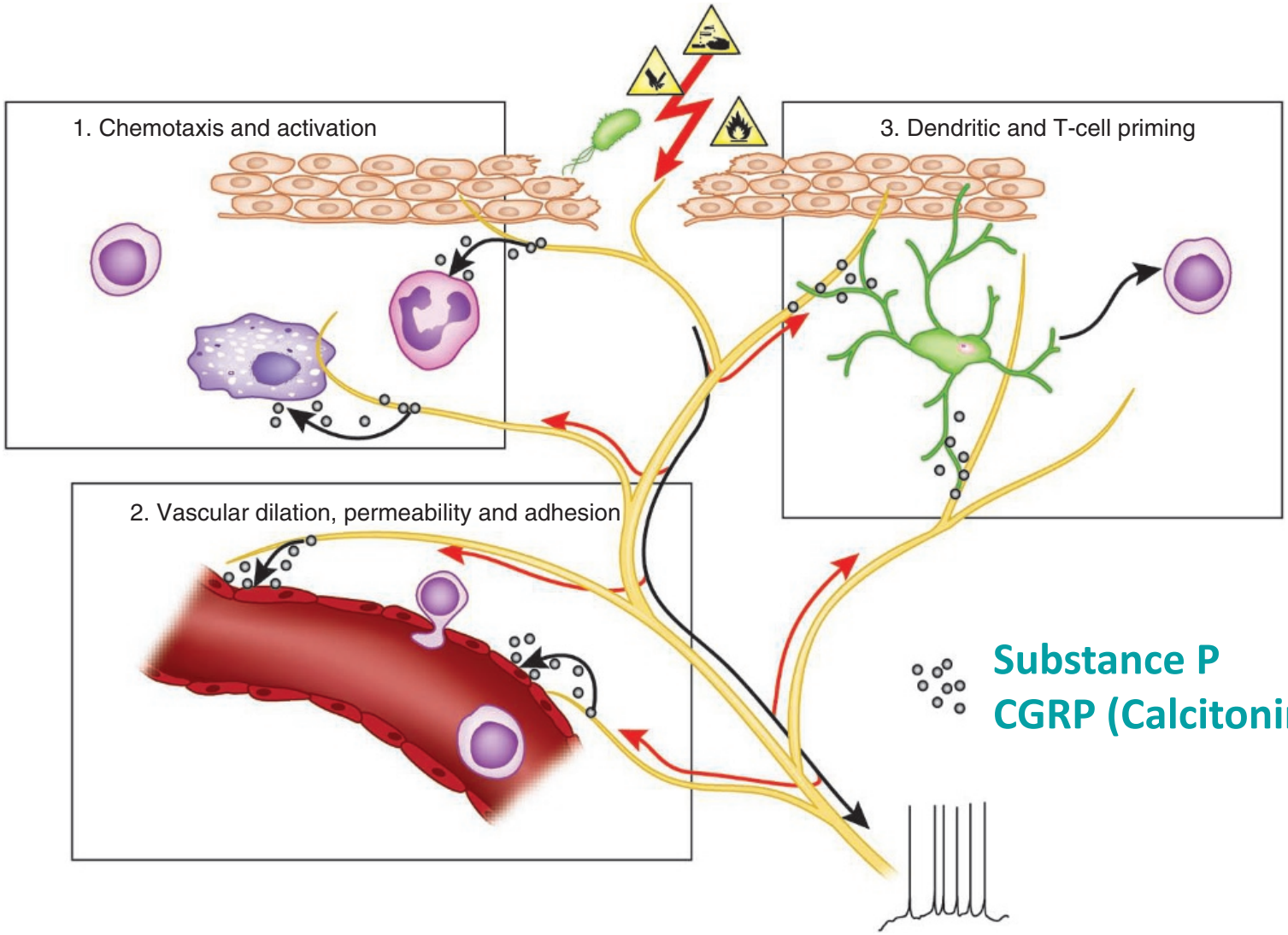
| Substances* | Concentrations | Wheal 20 min† | Erythema 20 min† | Erythema 24 h† |
|---|---|---|---|---|
| Histamine | 1 mg $mL^{-1}$ | • | ++ | + |
| Serotonin | 0.25 mg $mL^{-1}$ | • (4 of 5 dogs) | ++ (3 of 5 dogs) | – |
| | 1.00 mg $mL^{-1}$ | • | ++ | – |
| | 2.50 mg $mL^{-1}$ | • | +++ | NR |
| Tryptase (human lung) | 2 ng $mL^{-1}$ | – | – | – |
| | 8 ng $mL^{-1}$ | – | – | – |
| | 20 ng $mL^{-1}$ | – | – | NR |
| Substance P | 6.74 µg $mL^{-1}$ | – | – | – |
| | 26.96 µg $mL^{-1}$ | – | + (3 of 5 dogs) | – |
| | 67.4 µg $mL^{-1}$ | • (1 of 5 dogs) | + (3 of 5 dogs) | NR |
| IL-2 (human recombinant) | 0.40 mg $mL^{-1}$ | – | – | + (4 of 5 dogs) |
| | 1.60 mg $mL^{-1}$ | – | ++ (4 of 5 dogs) | ++ |
| Saline | 0.9% | – | – | – |

## *Pruritus*

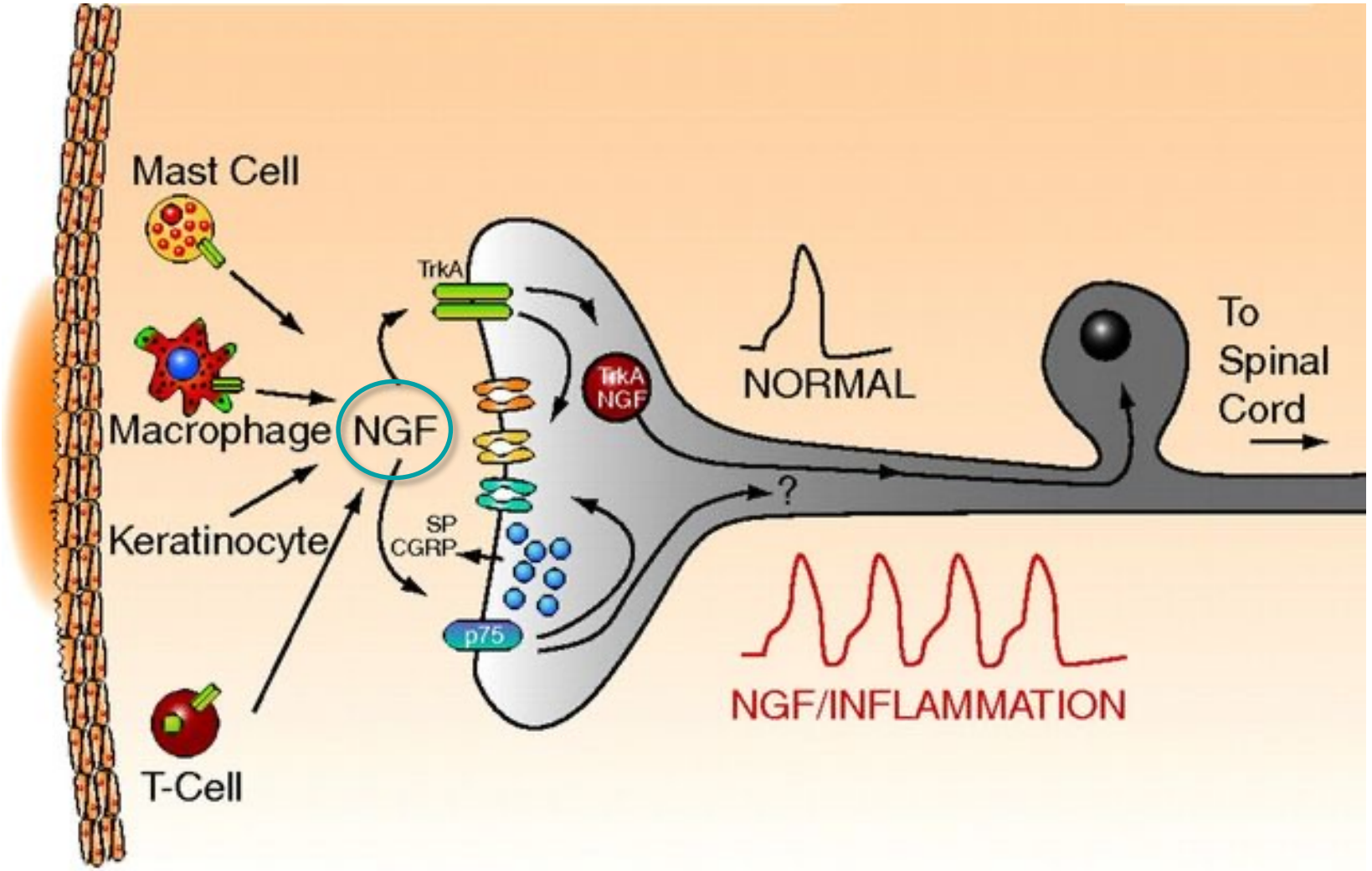
| Substances* | Amount† | Concentrations | Pruritus episodes‡ |
|---|---|---|---|
| Histamine | 0.05 mg | 1 mg $mL^{-1}$ | 1 |
| Serotonin | 0.013 mg | 0.25 mg $mL^{-1}$ | 6 |
| | 0.050 mg | 1.00 mg $mL^{-1}$ | 0 |
| | 0.125 mg | 2.50 mg $mL^{-1}$ | 6 |
| Tryptase (human lung) | 0.1 ng | 2 ng $mL^{-1}$ | 2 |
| | 0.4 ng | 8 ng $mL^{-1}$ | 6 |
| | 1.0 ng | 20 ng $mL^{-1}$ | 0 |
| Substance P | 0.337 µg | 6.74 µg $mL^{-1}$ | 0 |
| | 1.348 µg | 26.96 µg $mL^{-1}$ | 0 |
| | 3.370 µg | 67.4 µg $mL^{-1}$ | 0 |
| IL-2 (human recombinant) | 0.02 mg | 0.40 mg $mL^{-1}$ | 0, 1§ |
| | 0.08 mg | 1.60 mg $mL^{-1}$ | 1 |
| Saline | NA | 0.9% | 10 |
| Baseline | NA | NA | 2 |

Carr. 2009. *Vet Dermatol*

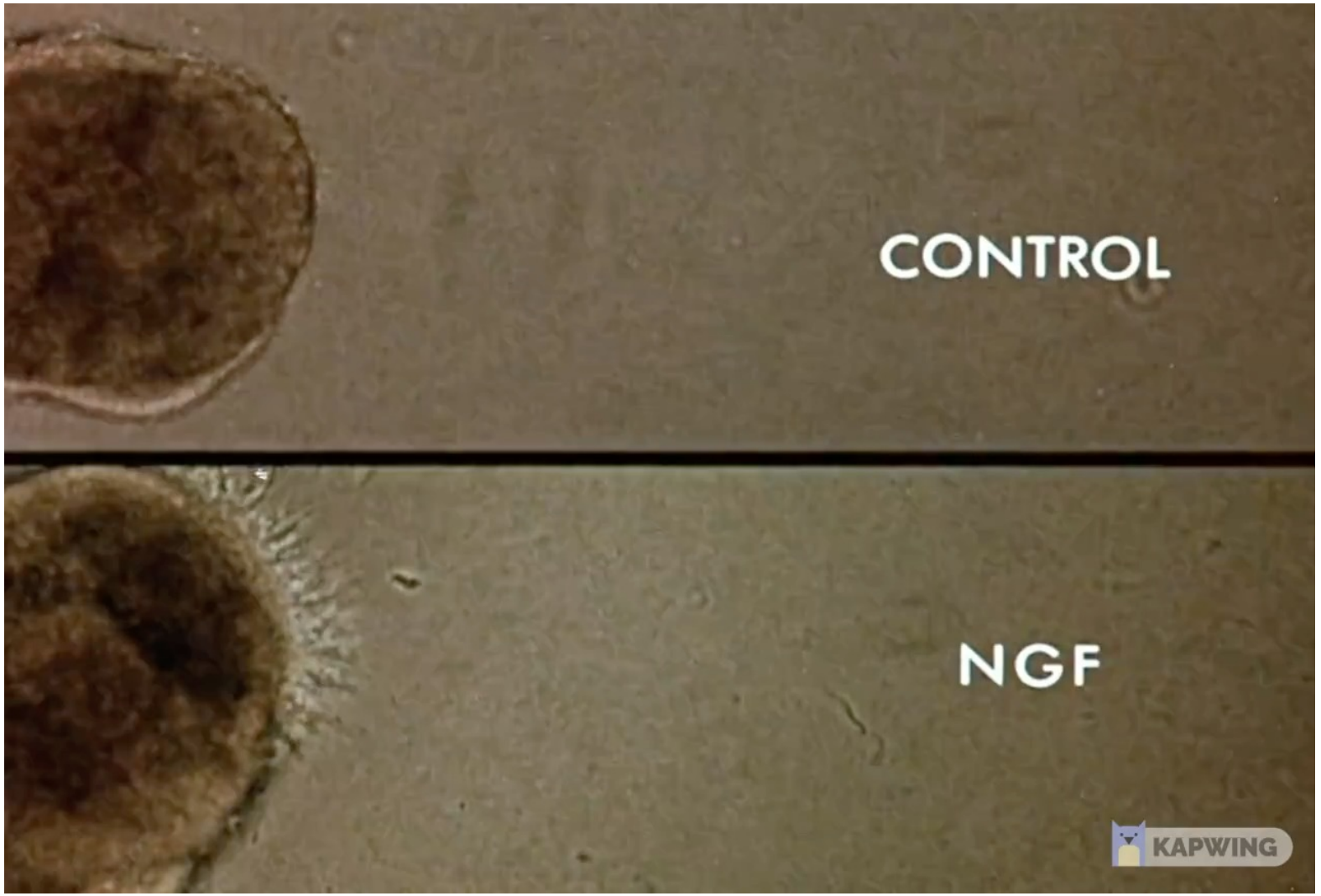
# Neurogenic Inflammation



# Neuropeptides – Nerve Growth Factor

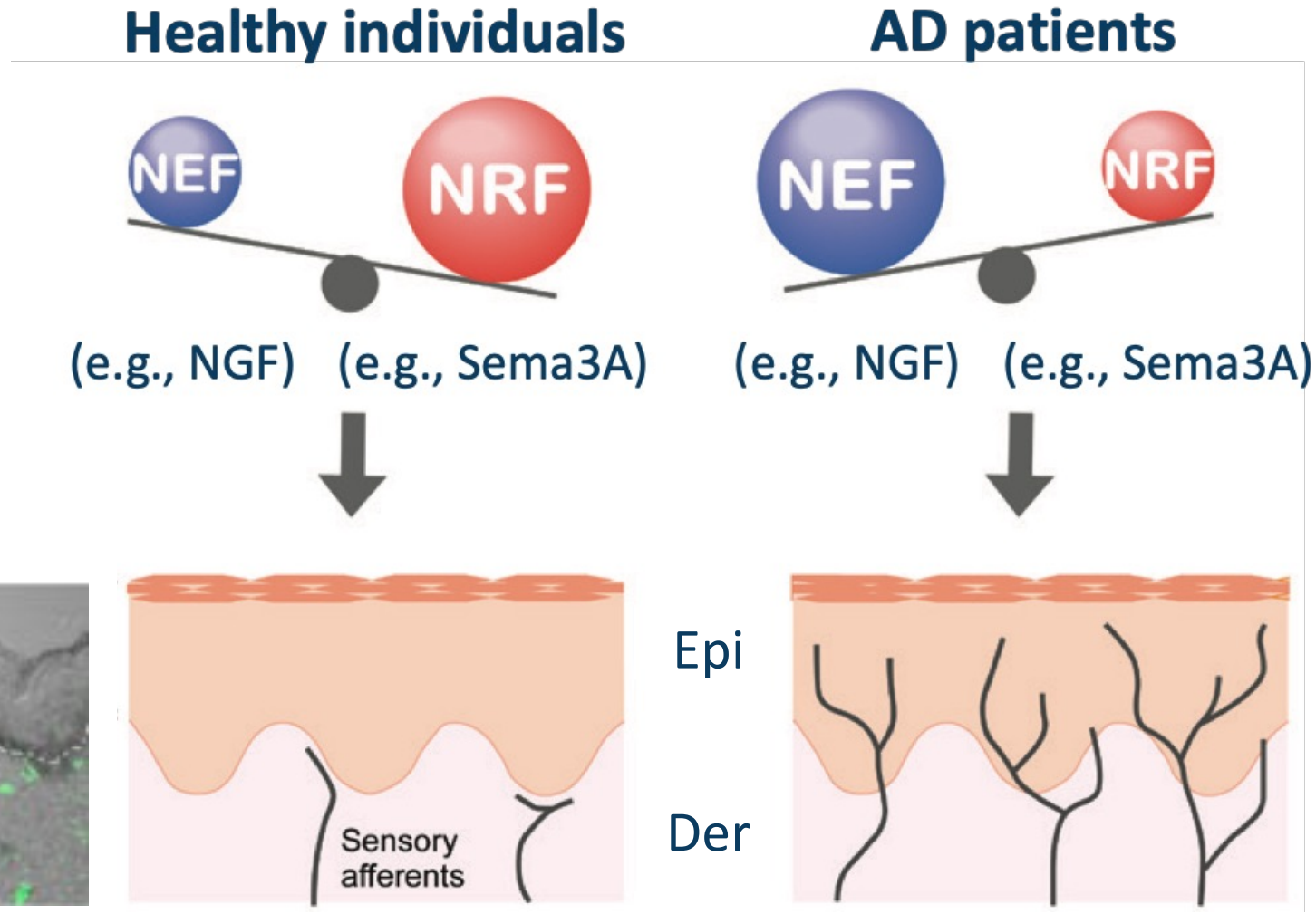


# Neuropeptides – Nerve Growth Factor

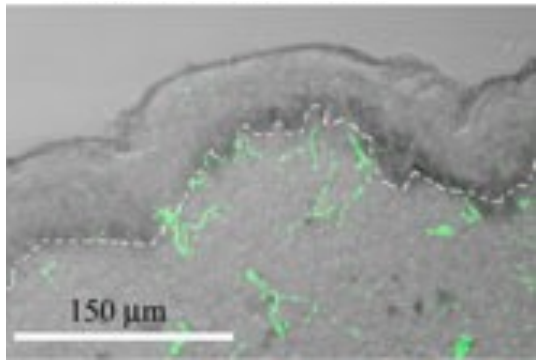


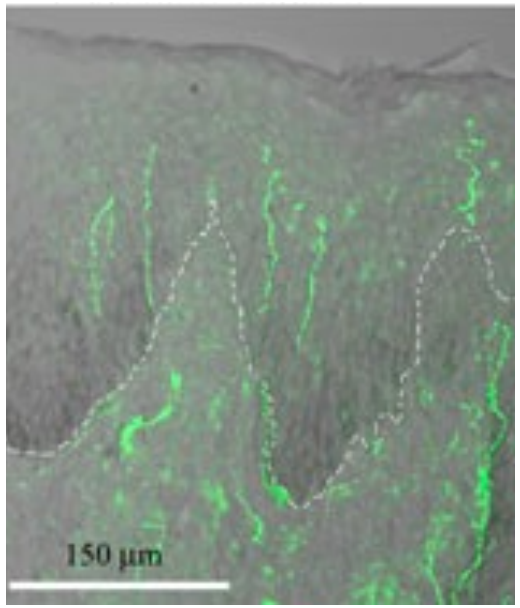

https://www.youtube.com/watch?v=t3PA-YbuJ5E

# Neurogenic Itch Sensation (Sensitive Skin)




*NEF: nerve elongation factor
*NRF: nerve repulsion factor



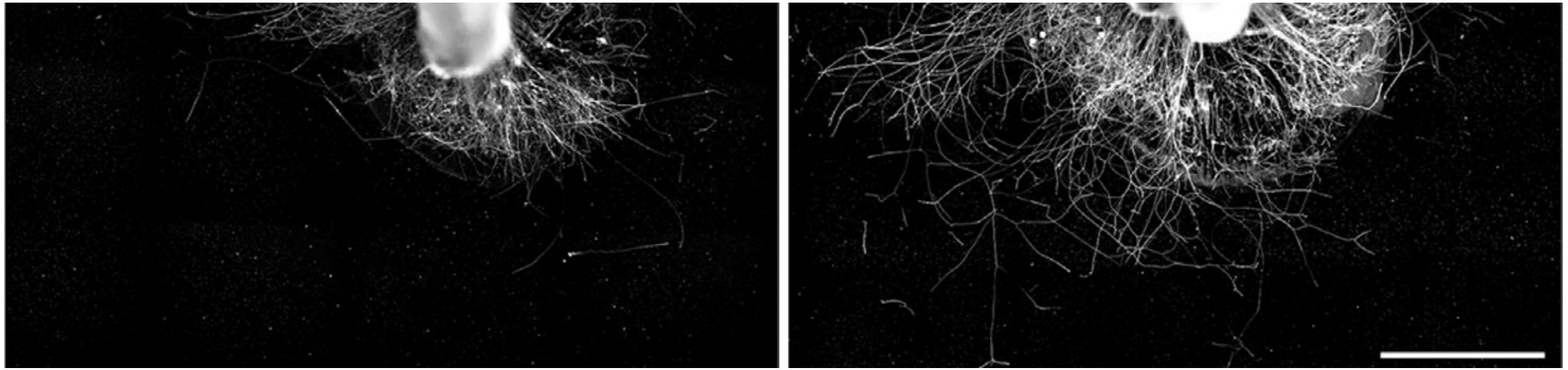

Kamo. 2016. *J Cosmet Dermatol;* Tominaga. 2014. *J Dermatol*

# Neurogenic Itch Sensation by IL-31?

*Mouse DRG neurons*

Control

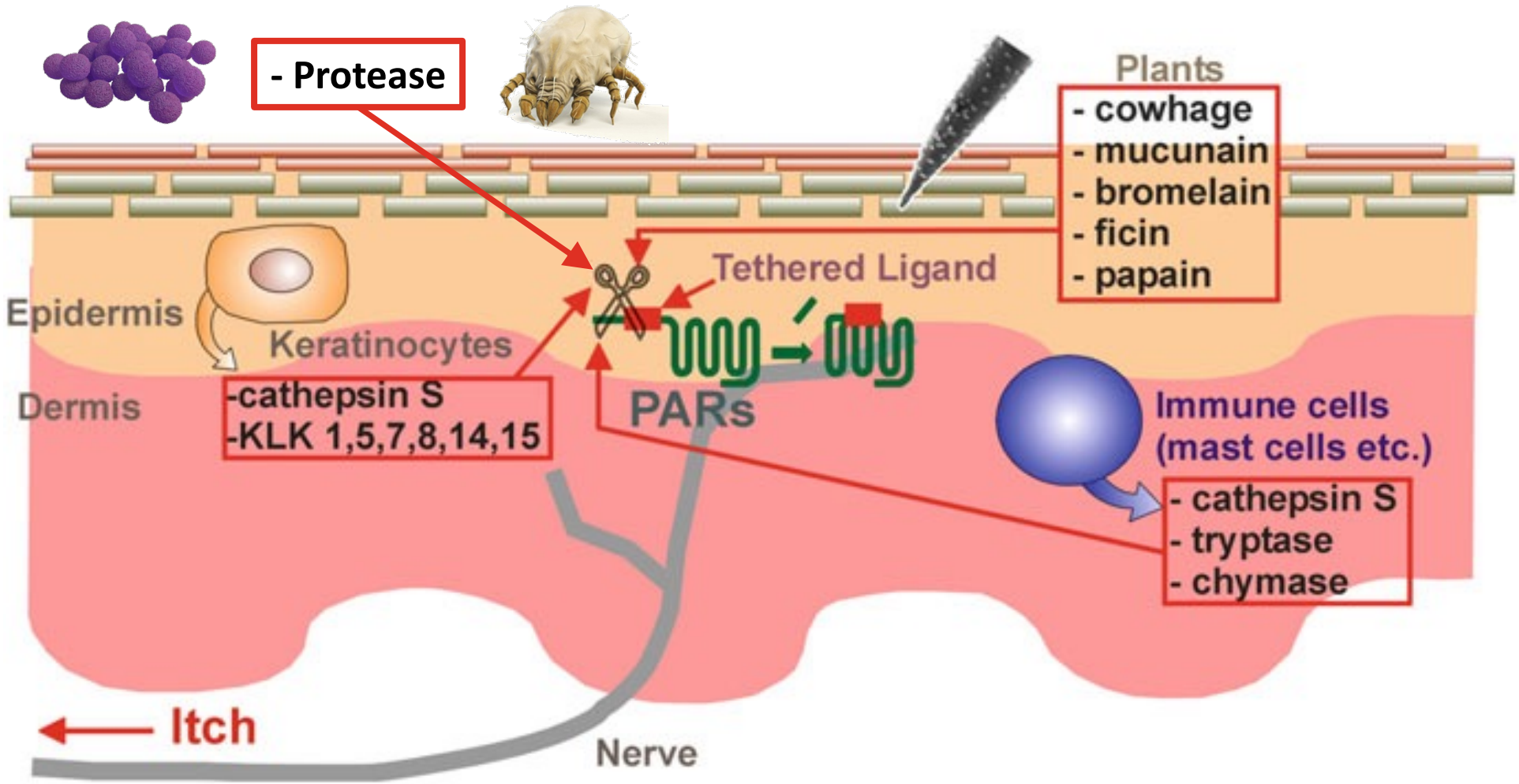
IL-31



✓ mIL-31 promotes axonal growth of DRG neurons

Fled. 2016. *J Allergy Clin Immunol*

# Proteases




*PARs: protease-activated receptors

# Does Protease Induce Pruritus in Dogs?

## *Wheal & Erythema*

| Substances* | Concentrations | Wheal 20 min† | Erythema 20 min† | Erythema 24 h† |
|---|---|---|---|---|
| Histamine | 1 mg $mL^{-1}$ | • | ++ | + |
| Serotonin | 0.25 mg $mL^{-1}$ | • (4 of 5 dogs) | ++ (3 of 5 dogs) | – |
| | 1.00 mg $mL^{-1}$ | • | ++ | – |
| | 2.50 mg $mL^{-1}$ | • | +++ | NR |
| Tryptase (human lung) | 2 ng $mL^{-1}$ | – | – | – |
| | 8 ng $mL^{-1}$ | – | – | – |
| | 20 ng $mL^{-1}$ | – | – | NR |
| Substance P | 6.74 µg $mL^{-1}$ | – | – | – |
| | 26.96 µg $mL^{-1}$ | – | + (3 of 5 dogs) | – |
| | 67.4 µg $mL^{-1}$ | • (1 of 5 dogs) | + (3 of 5 dogs) | NR |
| IL-2 (human recombinant) | 0.40 mg $mL^{-1}$ | – | – | + (4 of 5 dogs) |
| | 1.60 mg $mL^{-1}$ | – | ++ (4 of 5 dogs) | ++ |
| Saline | 0.9% | – | – | – |

## *Pruritus*

| Substances* | Amount† | Concentrations | Pruritus episodes‡ |
|---|---|---|---|
| Histamine | 0.05 mg | 1 mg $mL^{-1}$ | 1 |
| Serotonin | 0.013 mg | 0.25 mg $mL^{-1}$ | 6 |
| | 0.050 mg | 1.00 mg $mL^{-1}$ | 0 |
| | 0.125 mg | 2.50 mg $mL^{-1}$ | 6 |
| Tryptase (human lung) | 0.1 ng | 2 ng $mL^{-1}$ | 2 |
| | 0.4 ng | 8 ng $mL^{-1}$ | 6 |
| | 1.0 ng | 20 ng $mL^{-1}$ | 0 |
| Substance P | 0.337 µg | 6.74 µg $mL^{-1}$ | 0 |
| | 1.348 µg | 26.96 µg $mL^{-1}$ | 0 |
| | 3.370 µg | 67.4 µg $mL^{-1}$ | 0 |
| IL-2 (human recombinant) | 0.02 mg | 0.40 mg $mL^{-1}$ | 0, 1§ |
| | 0.08 mg | 1.60 mg $mL^{-1}$ | 1 |
| Saline | NA | 0.9% | 10 |
| Baseline | NA | NA | 2 |

Carr. 2009. *Vet Dermatol*

# Quiz!

**3. Which of the following cytokine has been demonstrated to cause itch in dogs and cats?**

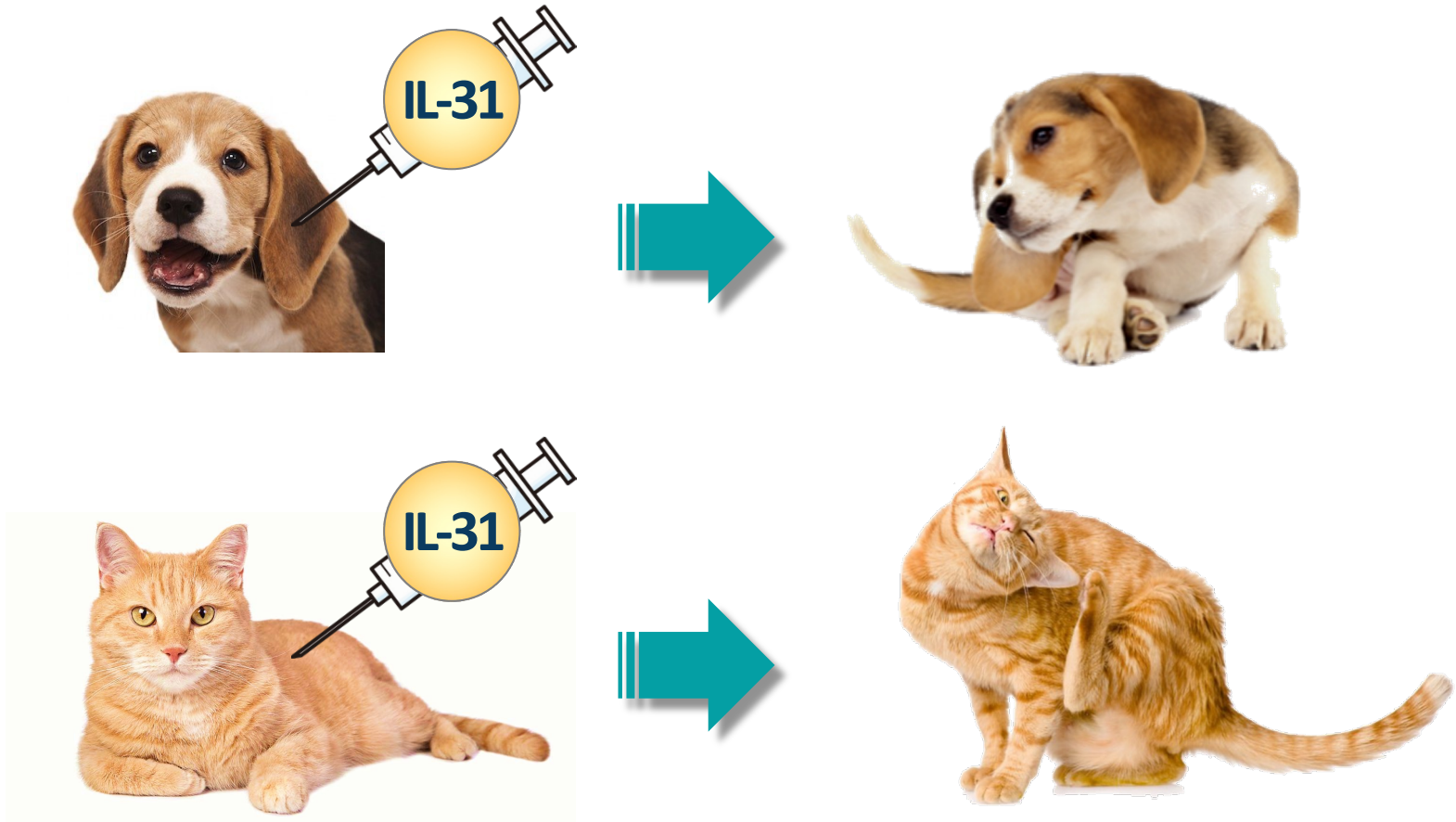
a. TSLP

b. IL-2

c. IL-31

d. IL-33

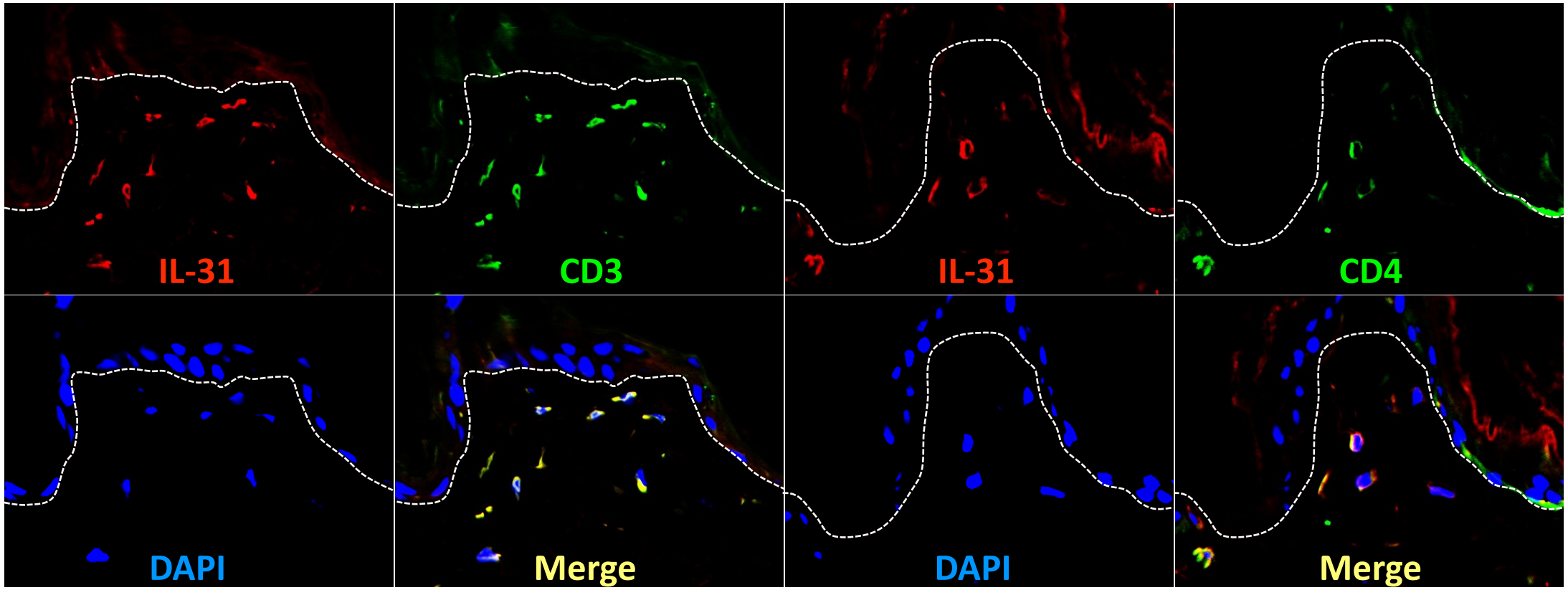
# Cytokines – IL-31




Gonzales. 2013. *Vet Dermatol*
Fleck. 2019. *NAVDF*

# IL-31 Producing Cells in Canine AD Skin

------ Epidermal-dermal borderline



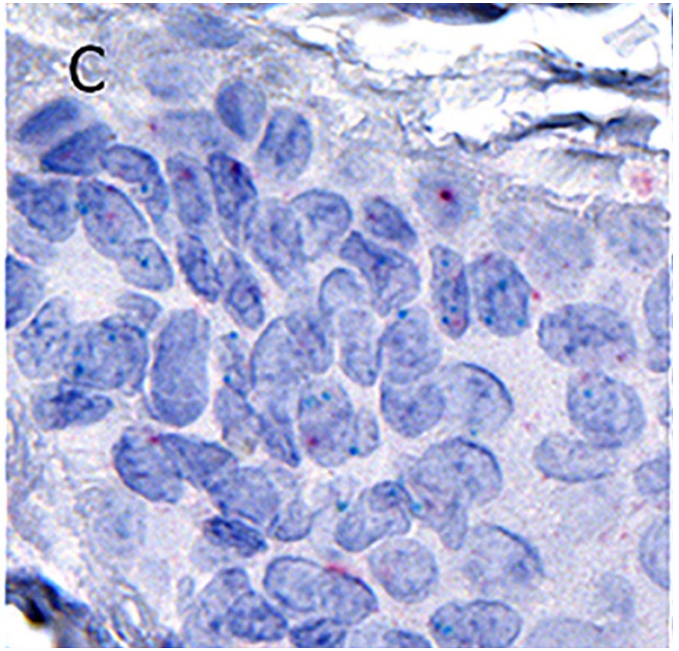

$IL\text{-}31^{+}CD3^{+}$ = 91-100%

$IL\text{-}31^{+}CD4^{+}$ = 63-100%

✓ $CD3^{+}CD4^{+}$ T cells (likely **Th2 cells**) produce IL-31

# Keratinocytes Produce IL-31?

## IL-31 mRNA ISH

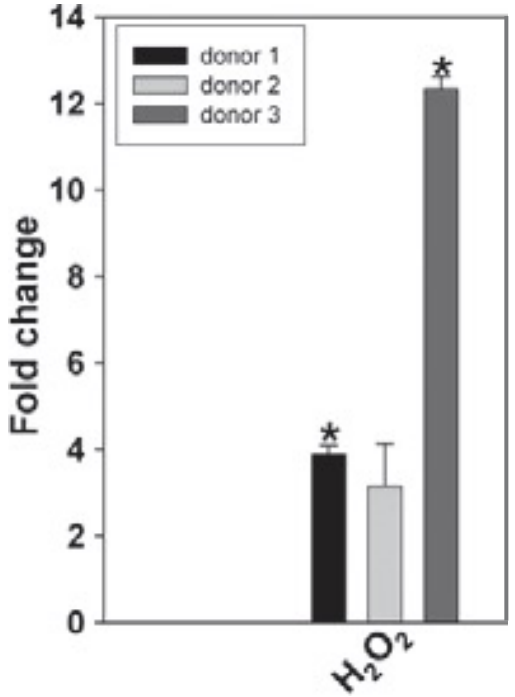



Canine AD Skin

**IL-31 mRNA (+)**

Shiomitsu. 2021. *Res Vet Sci*

## *IL-31 mRNA qPCR*



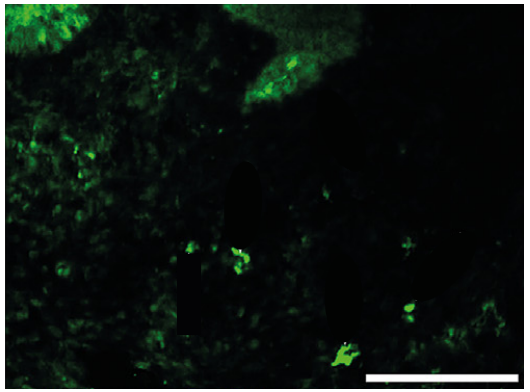

Normal human KC

**IL-31 mRNA (+)**

Cornelissen. 2011. *Br J Dermatol*

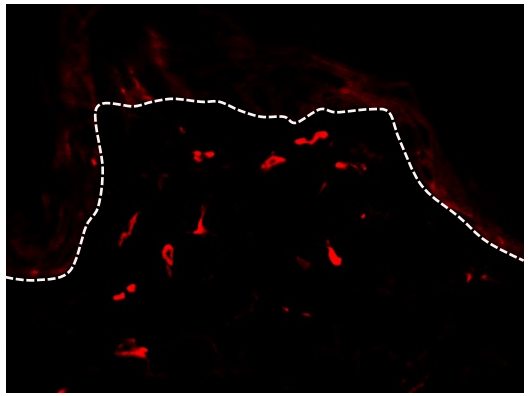
## *IL-31 IF*

Human AD skin



**IL-31 (-)**

Canine AD skin



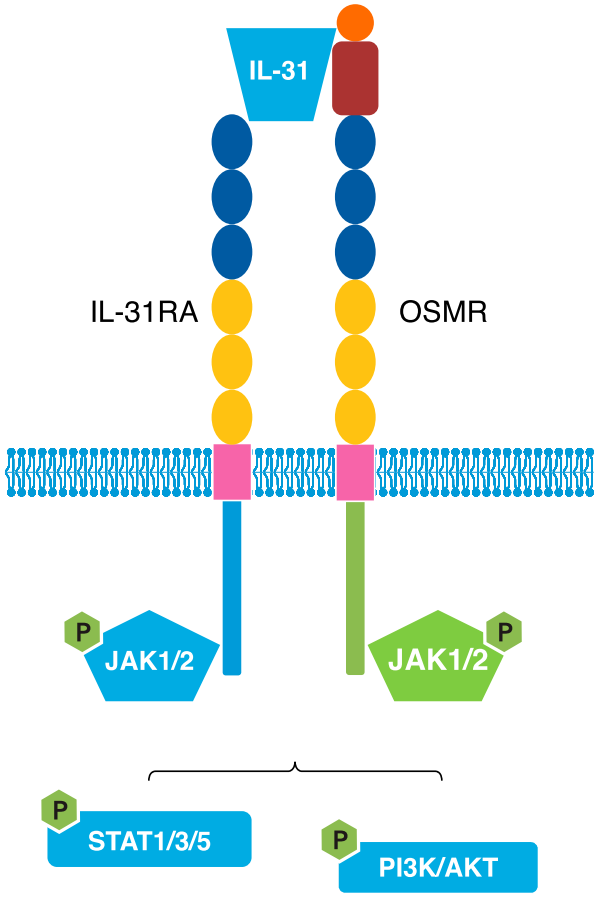
**IL-31 (-)**

Cevikbas. 2014. *J Allergy Clin Immunol*

Tamamoto-Mochizuki. 2019. *Vet Dermatol*

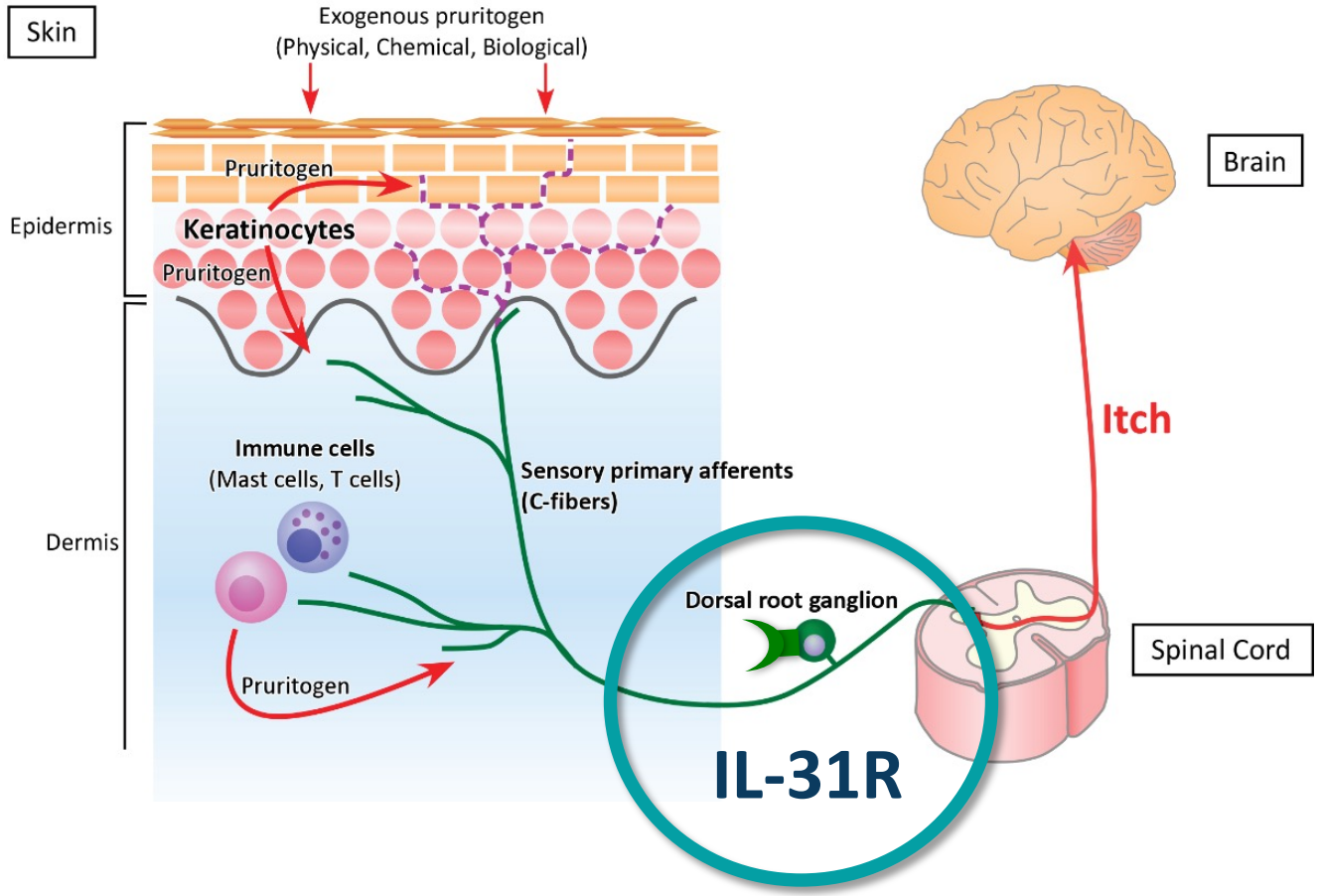
# Which Cells Receive IL-31 Signals?

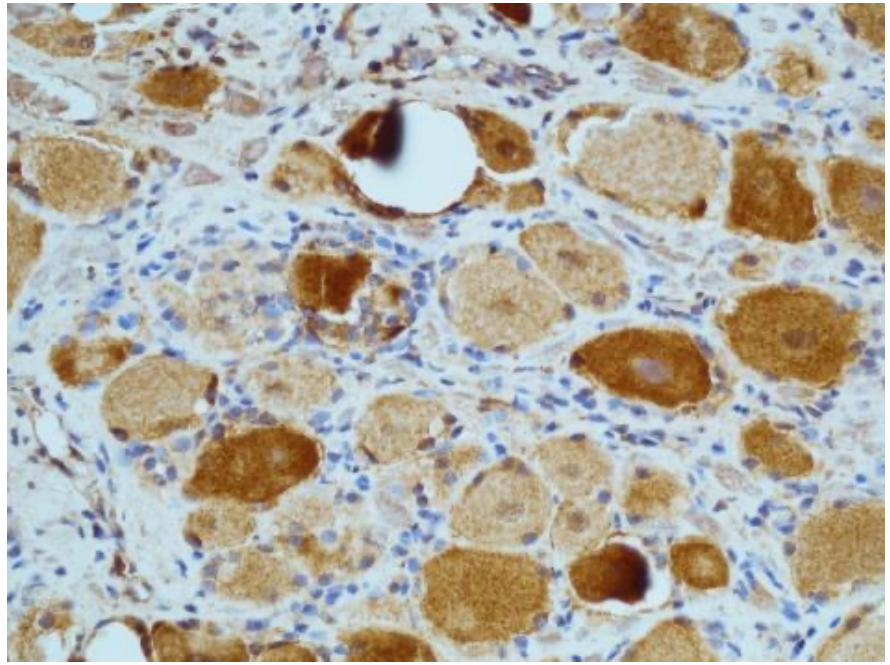
## *IL-31RA receptor*




Feretti. 2017. *J Leukoc Biol*

# Which Cells Receive IL-31 Signals?



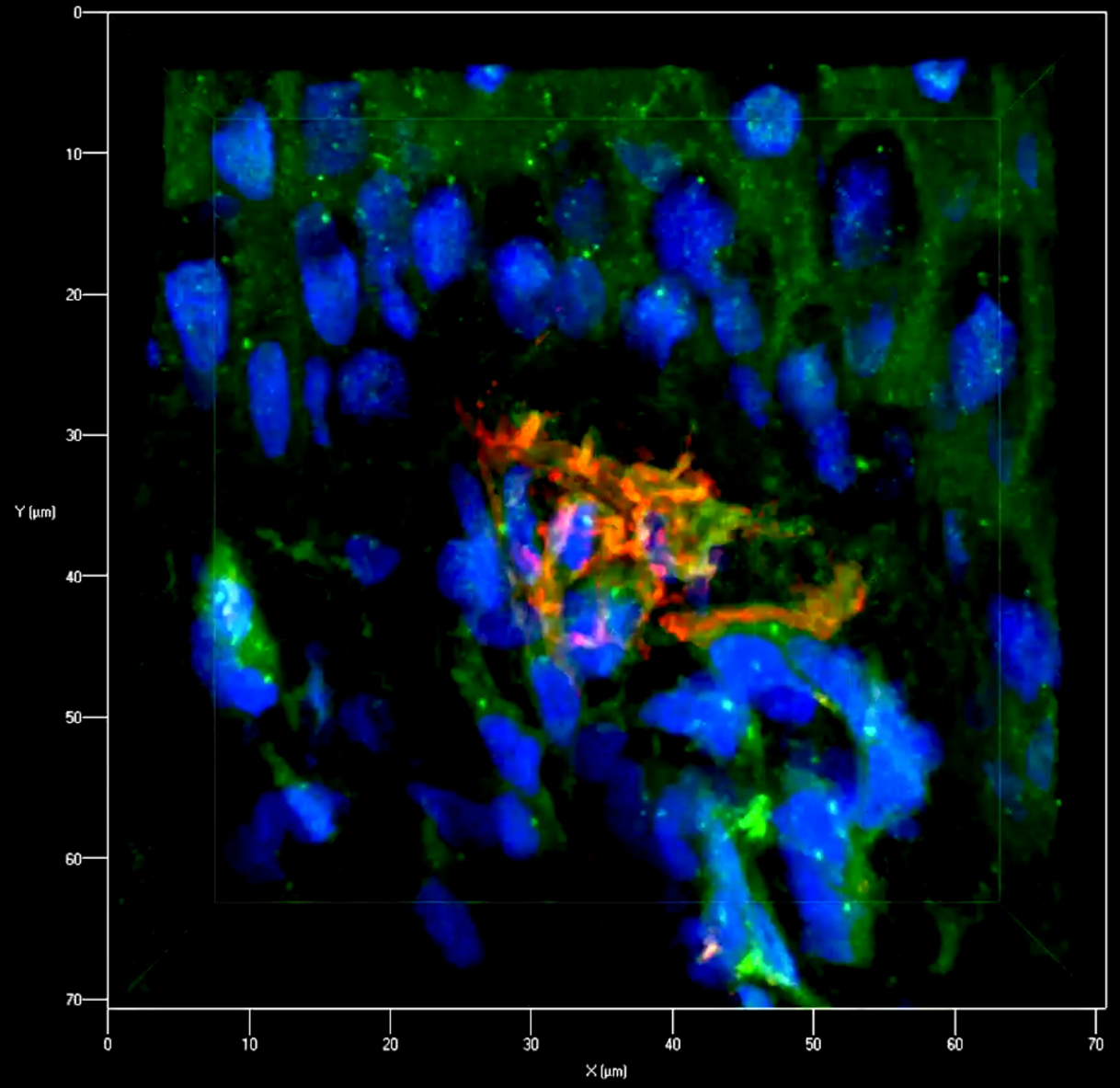
IL-31RA (+) neurons in canine DRGs

Bammert. 2016. *WCVD*

# IL-31RA/β3T Double-IF

Canine nasal planum

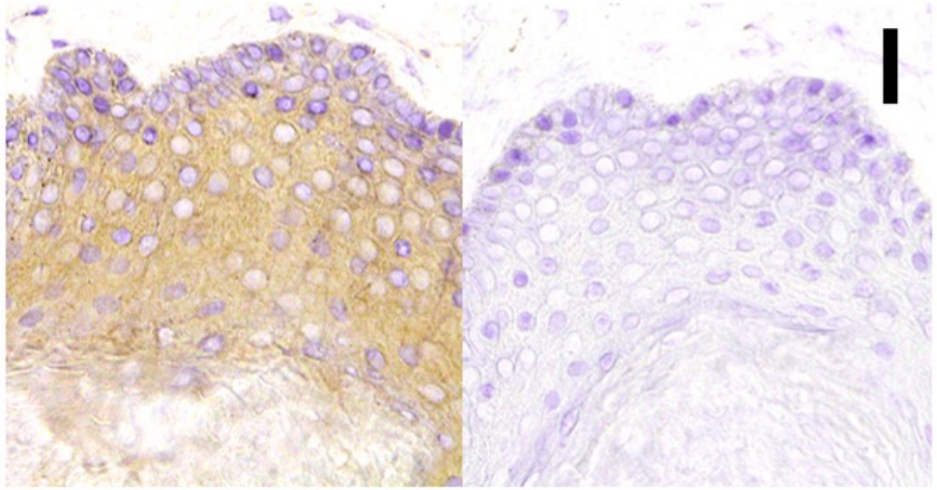
**β3-tubulin** (nerve marker)
**IL-31RA** (IL-31 receptor)




Tamamoto-Mochizuki. 2021. *Vet Dermatol*

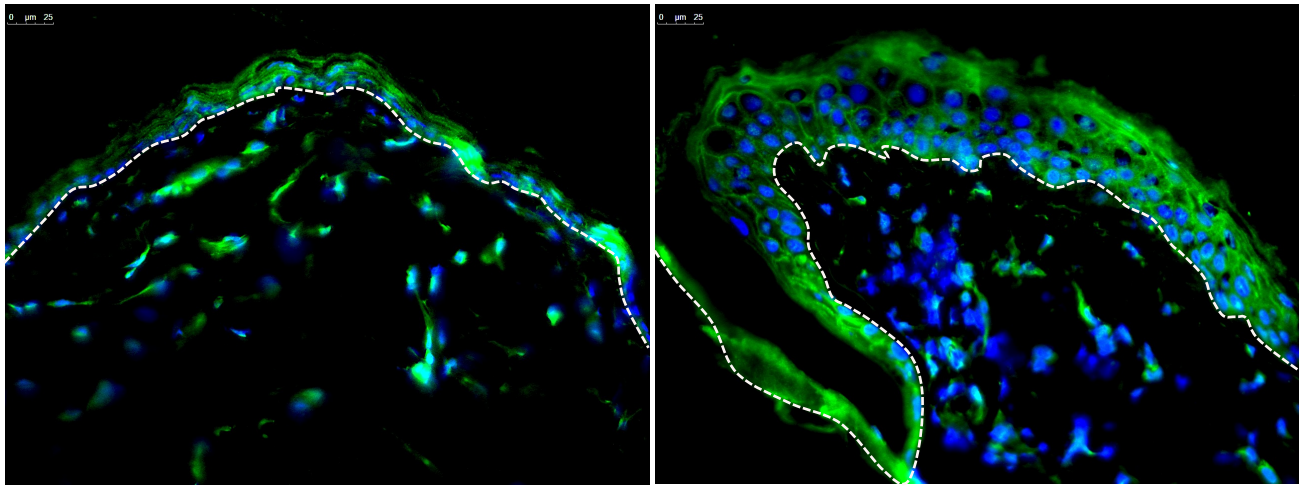
# Which else Cells Receive IL-31 Signals?

*IL-31RA IHC*: Human AD epidermis



**IL-31RA (+)** Isotype control

*IL-31RA IF*: Canine AD epidermis



Before AD flare
**IL-31RA (+)**

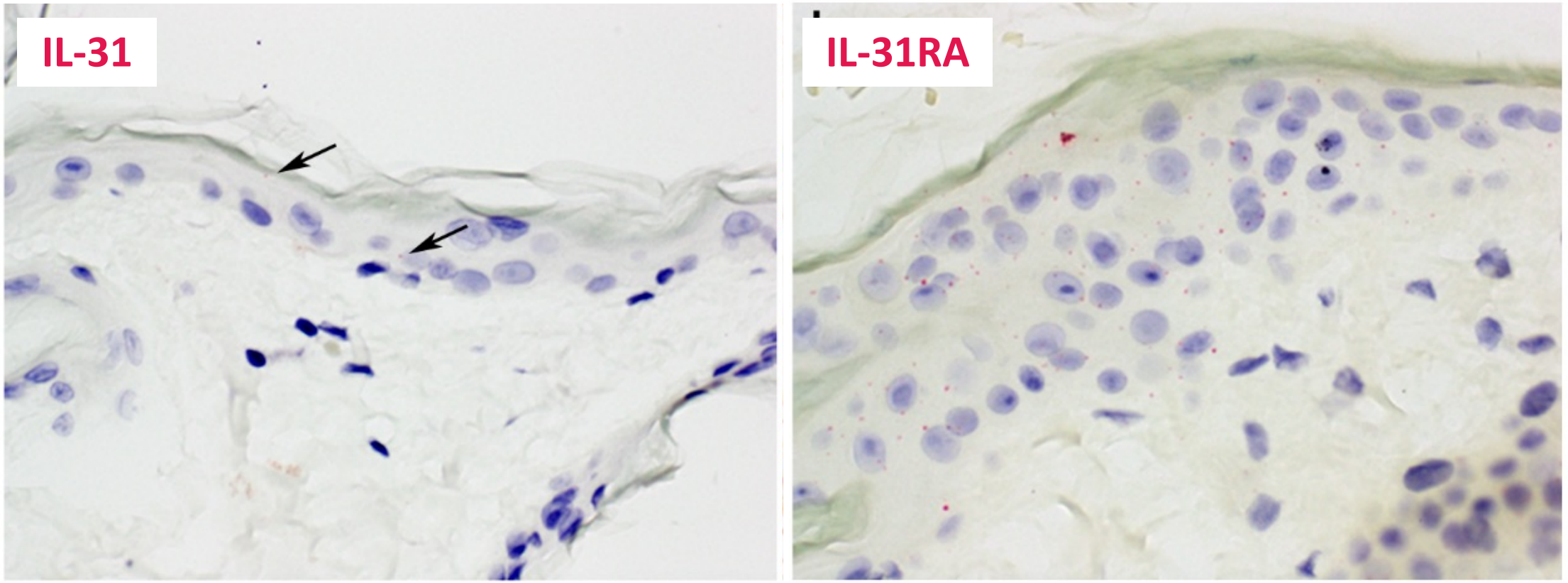
After AD flare
**IL-31RA (+)**

✓ IL-31RA was constitutively expressed on **keratinocytes**

Kato. *J Dermatol Sci* 2014; Tamamoto-Mochizuki. 2021. *Vet Dermatol*

# IL-31 in Feline Atopic Skin Syndrome

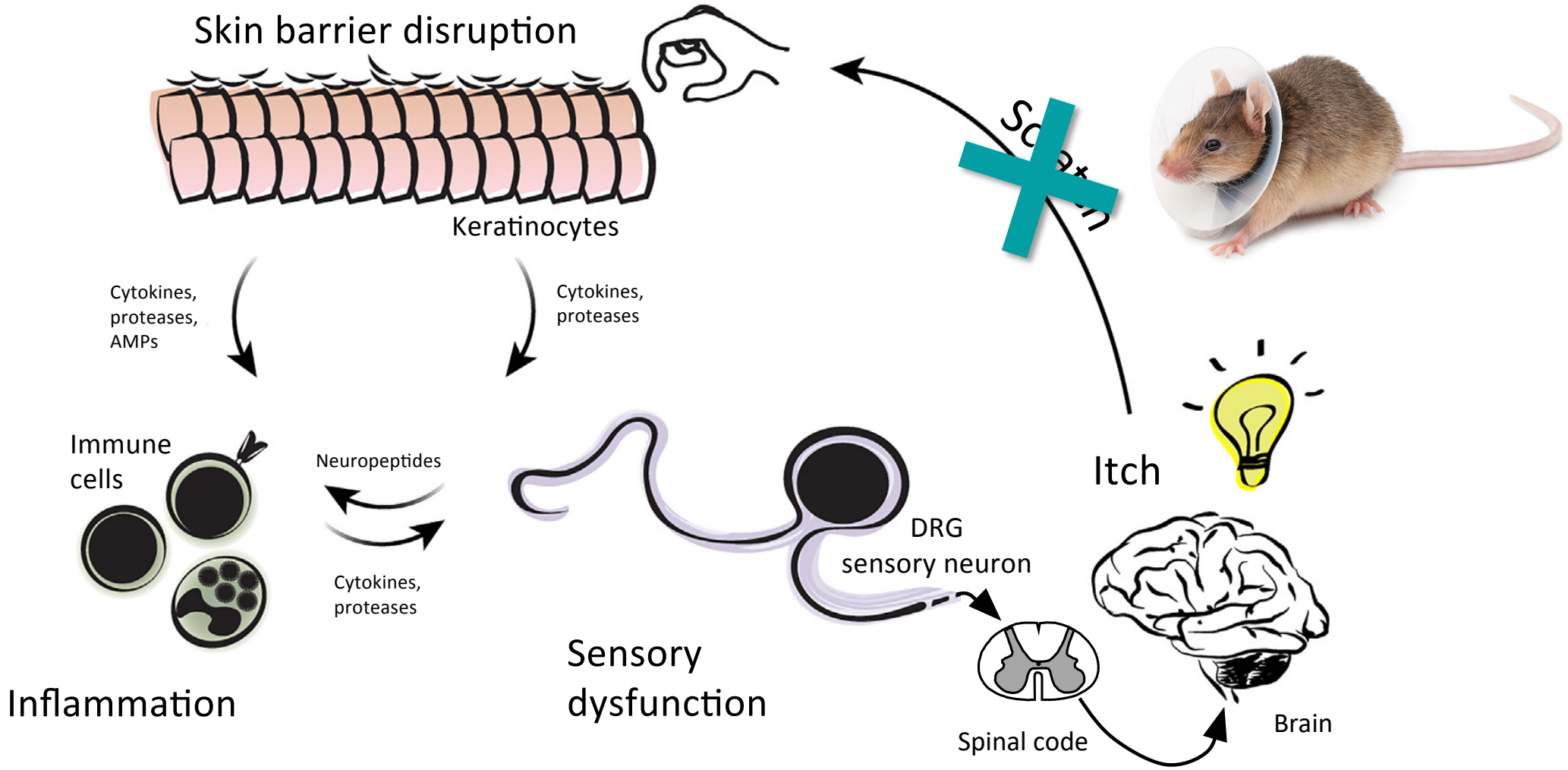
*IL-31/IL-31RA mRNA in situ hybridization*



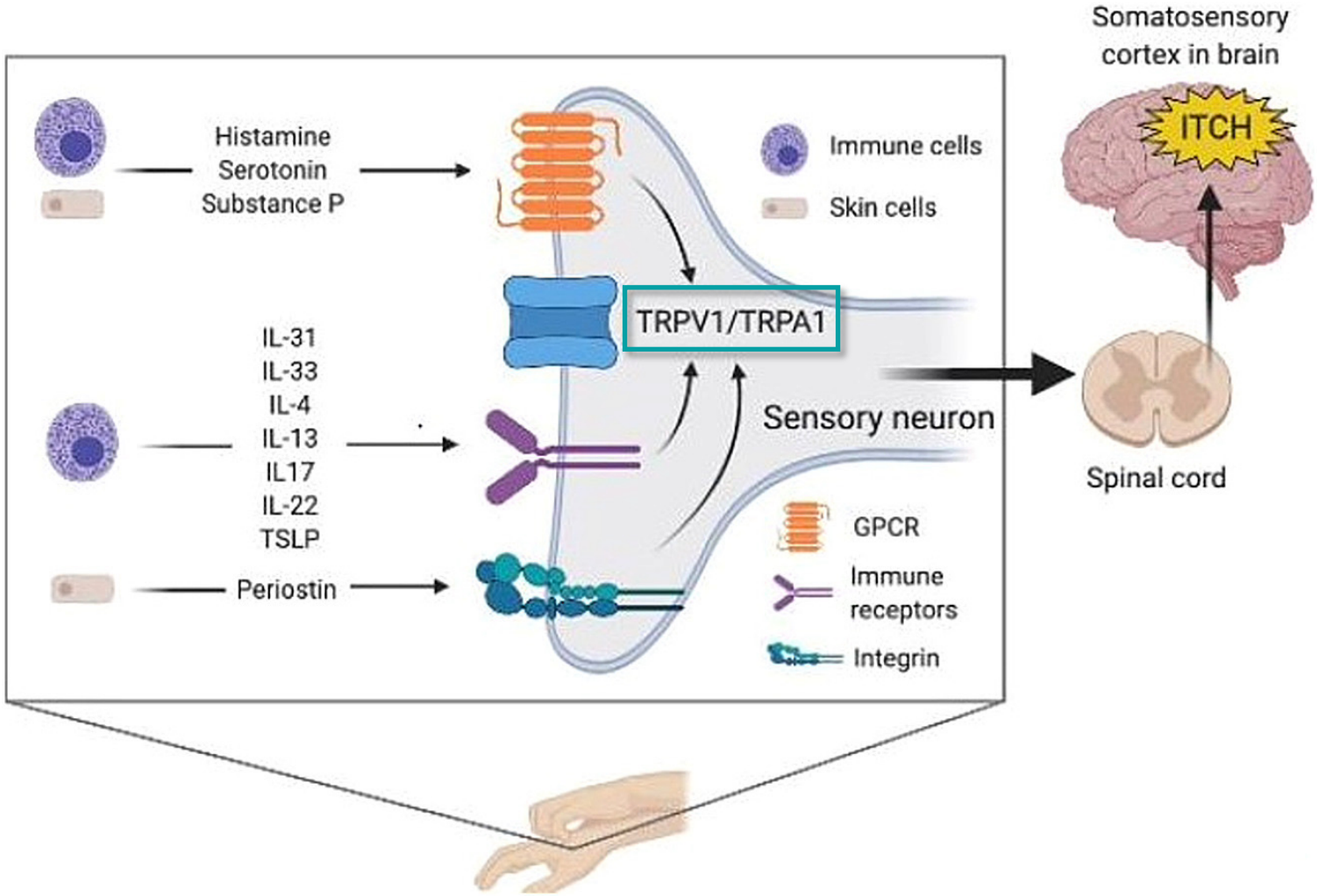

✓ Extremely low expression

Older. 2021. *Vet Dermatol*

# Itch-Scratch-Itch Cycle



# TRP in Itch Neuronal Pathway



# Quiz!

**4. Which of the following molecule is responsive for neurogenic inflammation?**

a. Substance P

b. TRPV1

c. Tryptase

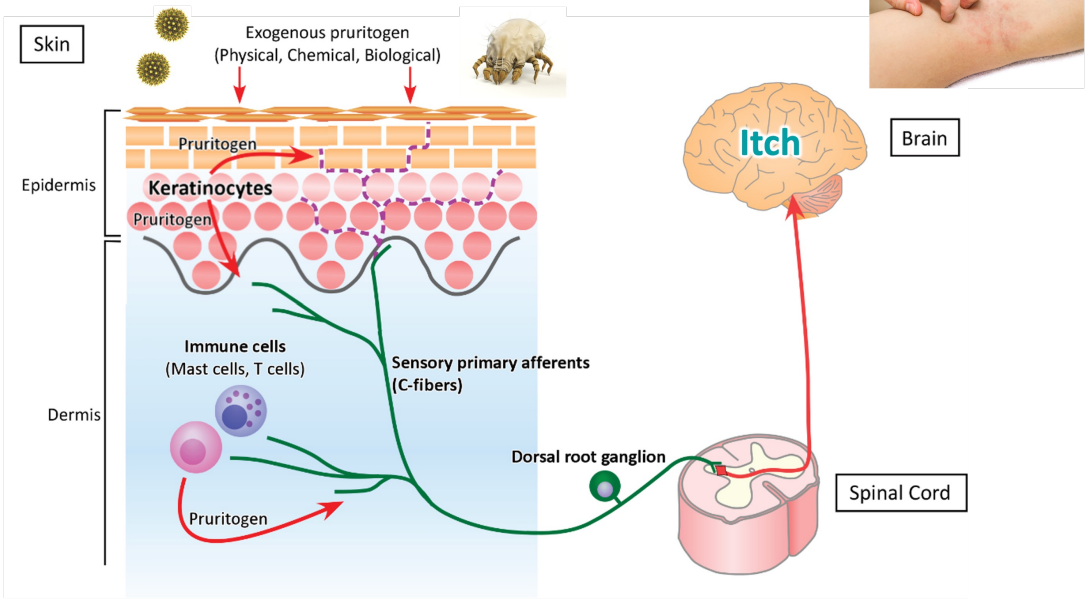
d. IL-31

# 3. Diagnosis of Neuropathic/Psychogenic Skin Diseases

# Neurogenic Itch

Itch induced by pruritogens in the absence of neural damage

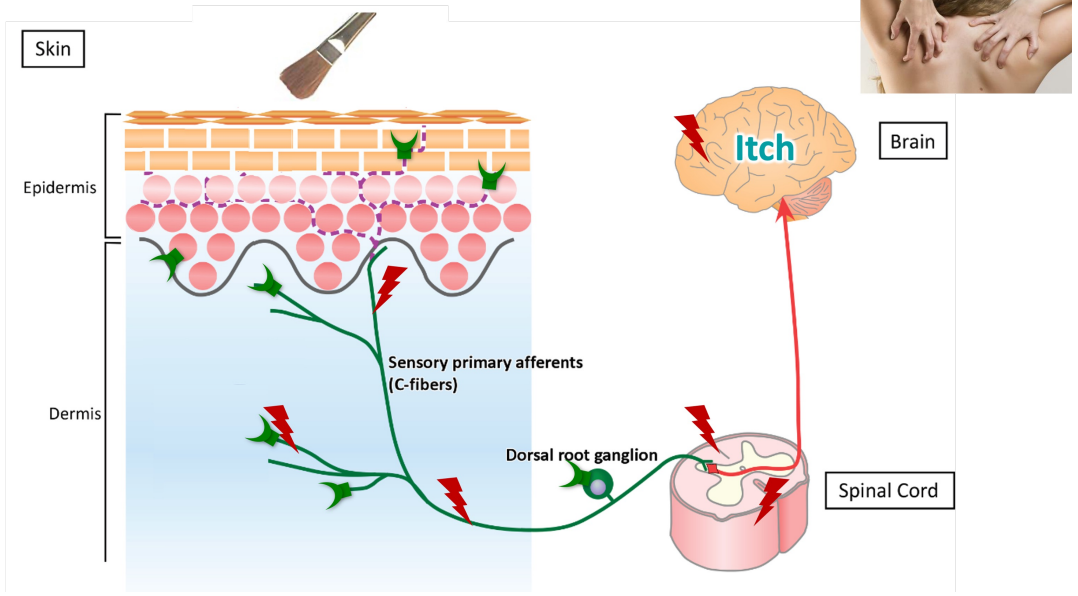
**Itch on *Inflamed Skin***



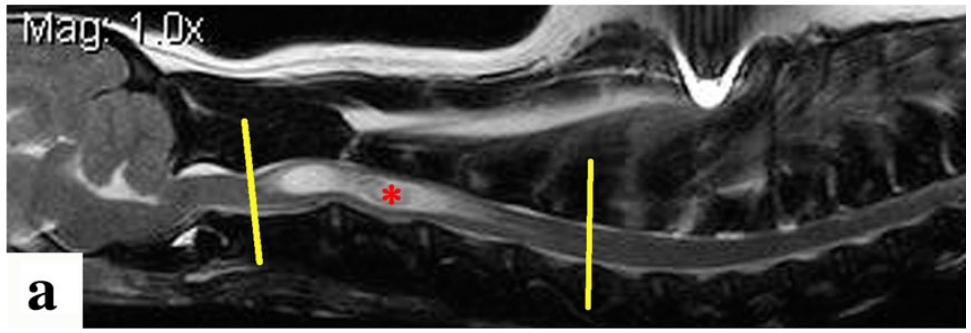

# Neuropathic Itch

Itch associated with damaged neurons

**Itch on *Non-Inflamed Skin***



# Neuropathic Itch – Canine Syringomyelia (SM)




"**Phantom scratching**" = Dysesthesia
: spontaneous or evoked unpleasant sensation

- Breeds - CKCS
- Causes - Alteration of sensory threshold? (spongy degenerative change of spinal cords)
- Diagnosis - Clinical presentation, MRI

Plessas. 2012. *Vet Rec*; Nalborczyk. 2017. *Vet Res*

# Neuropathic Itch – Canine Syringomyelia (SM)

- 9 CKCS with SM + phantom scratching
- 20 control dogs


## Mechanical sensory threshold (MST)

| (a) | Cases | Controls | *P* |
|---|---|---|---|
| Median MST | 0.9 (0.06–175.7 [175.1]) | 0.24 (0.02–175.2 [5.1]) | 0.25 |
| Initial MST | 0.6 (0.04–350 [349.8]) | 0.16 (0.02–10 [0.3]) | 0.09 |
| Contralateral MST | 0.4 (0.04–15 [1.3]) | 0.07 (0.02–350 [5.3]) | 0.99 |

No difference between SM and control dogs

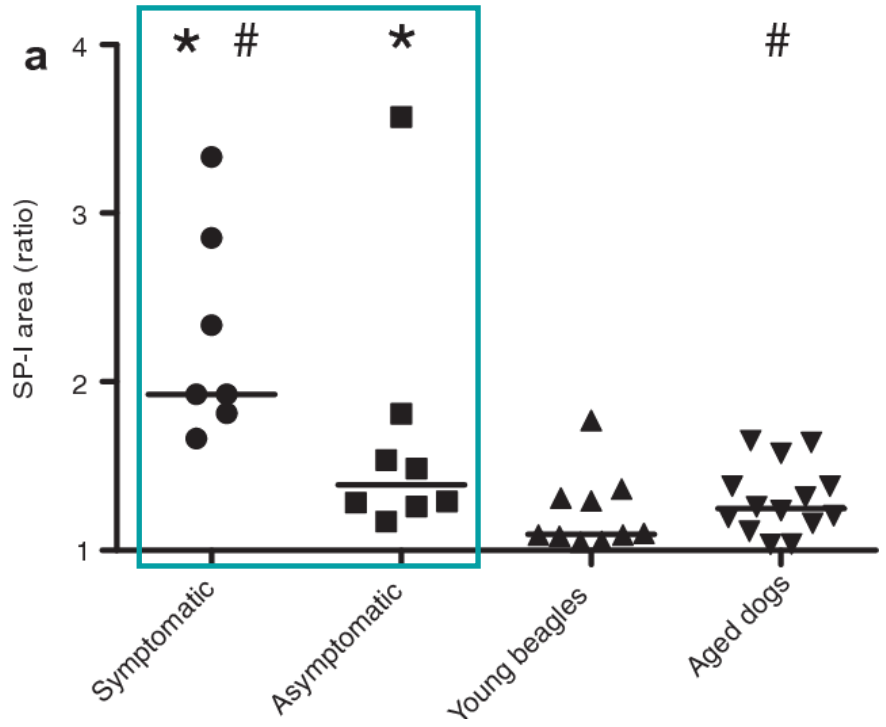
= *No difference in sensory thresholds*

Thoefner. 2019. *Vet J*

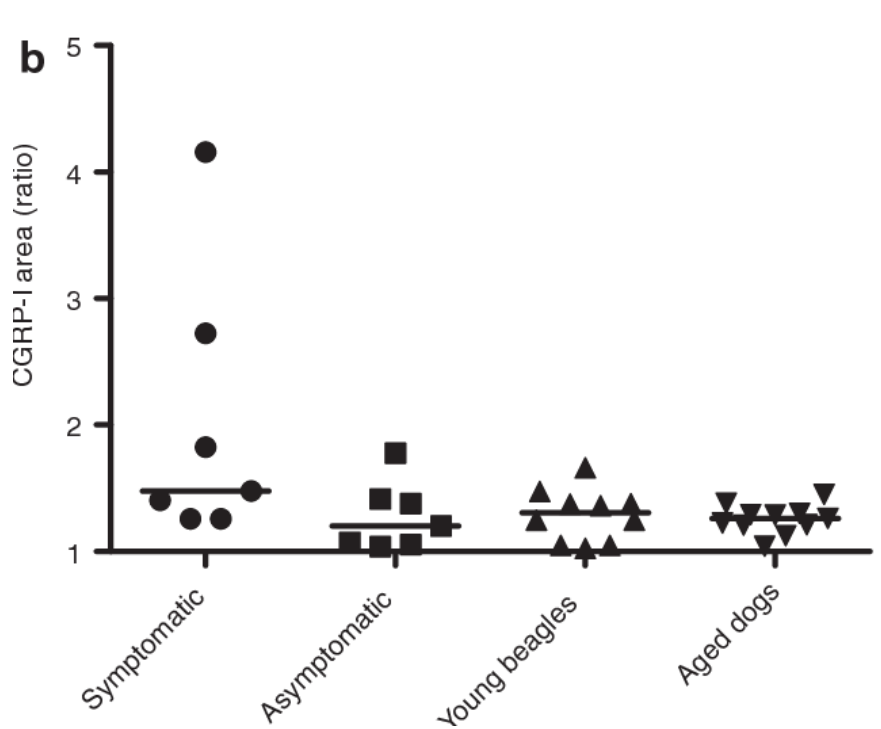
# Neuropathic Itch – Canine Syringomyelia (SM)

- Canine spinal cord tissues: CKCS + SM (symptomatic/asymptomatic)

SP




CGRP

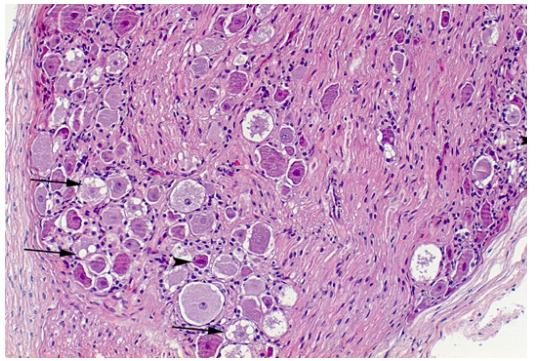



Significant difference of **SP** between symptomatic SM and control dogs
(No difference between symptomatic and asymptomatic)

Hu. 2012. *Res Vet Sci*

# Neuropathic Itch – Acral Mutilation Syndrome

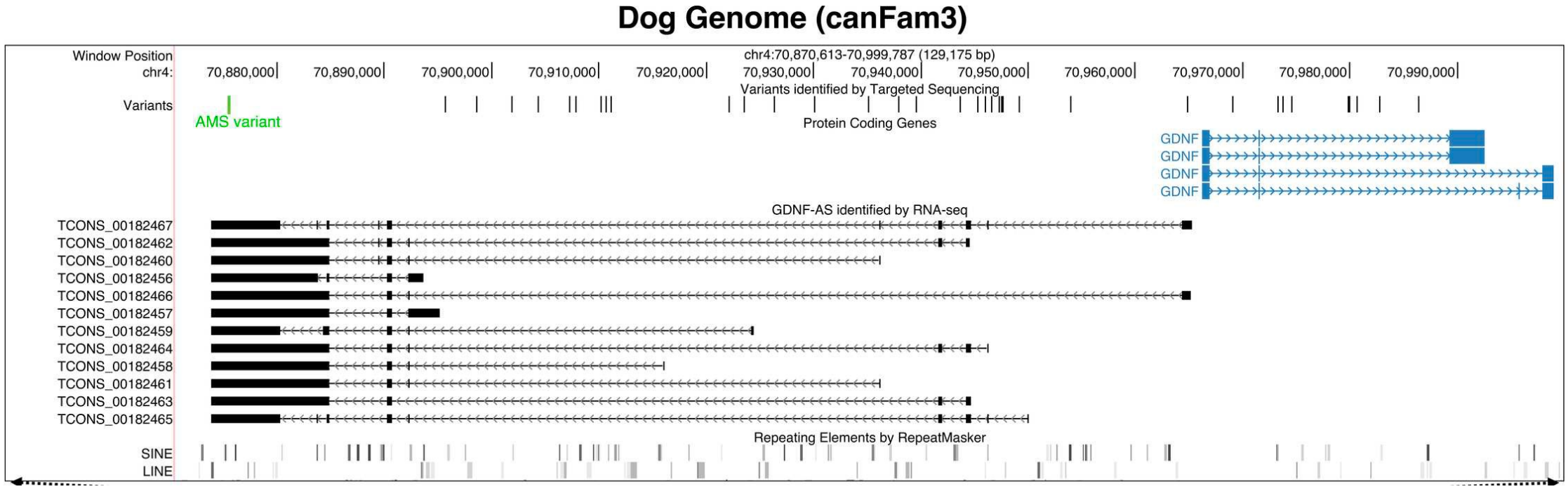

- Cause
  - *autosomal-recessive* sensory neuropathy (diminution of pain perception)
- Clinical presentation
  - sudden intense licking → auto-amputation
- Breeds - German short-haired pointer, English springer spaniel, English/French spaniel
- Mean age - 4 months
- Diagnosis - by clinical signs
- Prognosis - poor



Reduced number of neurons

# Neuropathic Itch – Acral Mutilation Syndrome

- SNP mutations at lincRNA upstream of ***GDNF*** = *GDNF-AS*



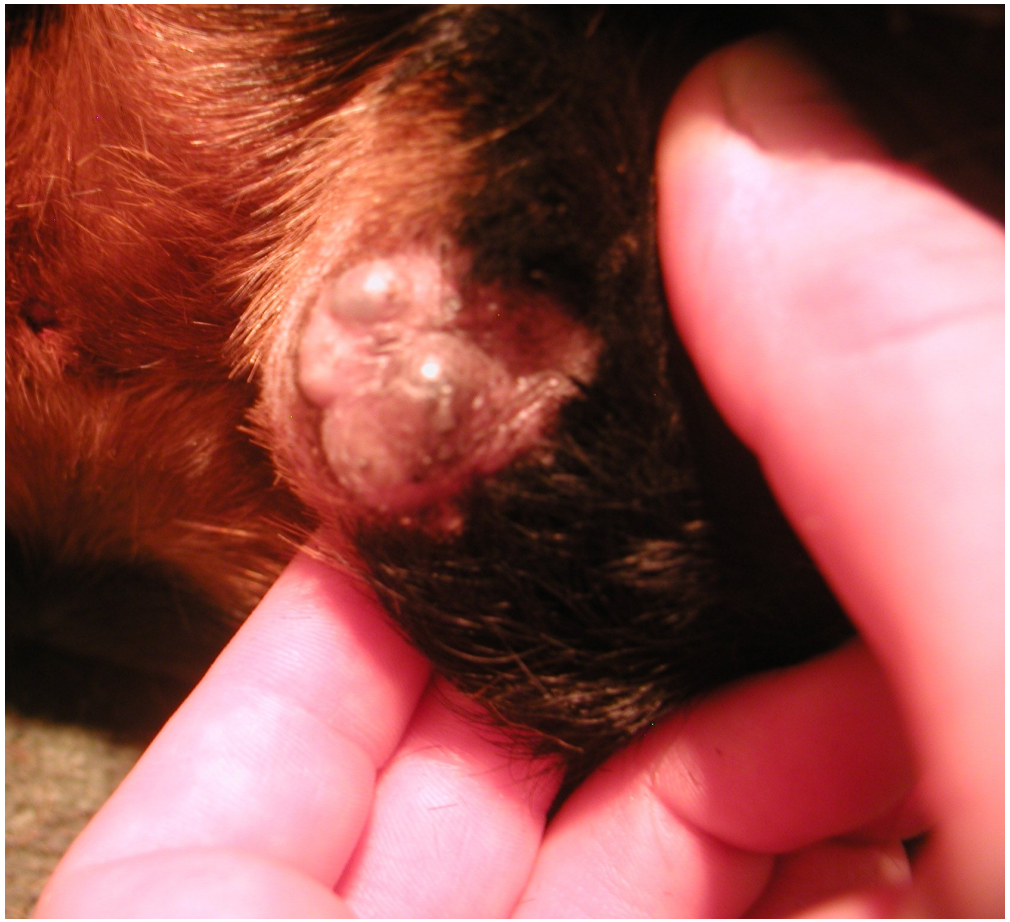

*GDNF* (glial cell derived neurotrophic factor)
**:** a small protein that promotes the survival of many types of neurons

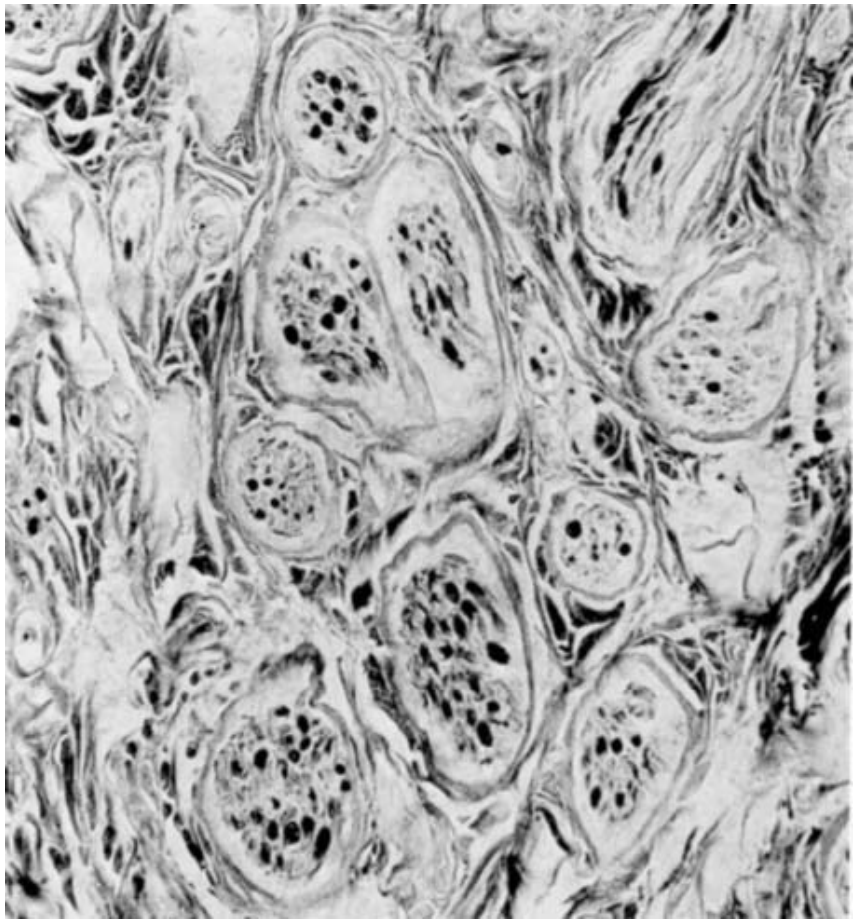
*LincRNA* (long noncoding RNA)
: >200 nucleotides at intron (not translated) that might regulate gene expression

Plassais. 2016. *PLoS Genet*

# Neuropathic Itch – Tail Dock Neuroma

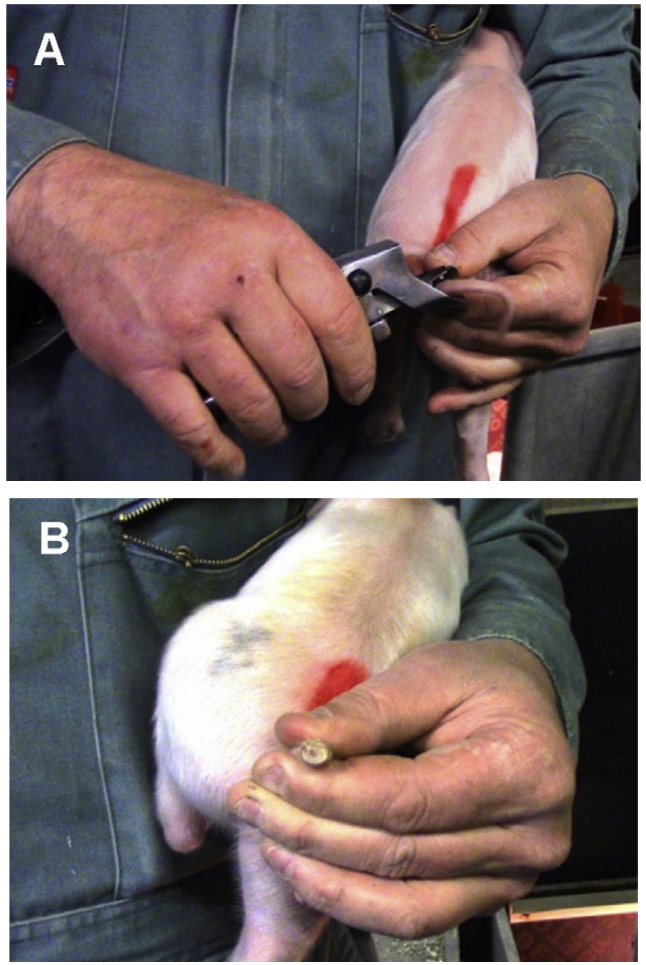
- Regenerative growth of nerves (neuroma) → pain → tail biting





Gross. 1990. *Vet Pathol*

# Neuropathic Itch – Tail Dock Neuroma




Tail docking by a hot iron

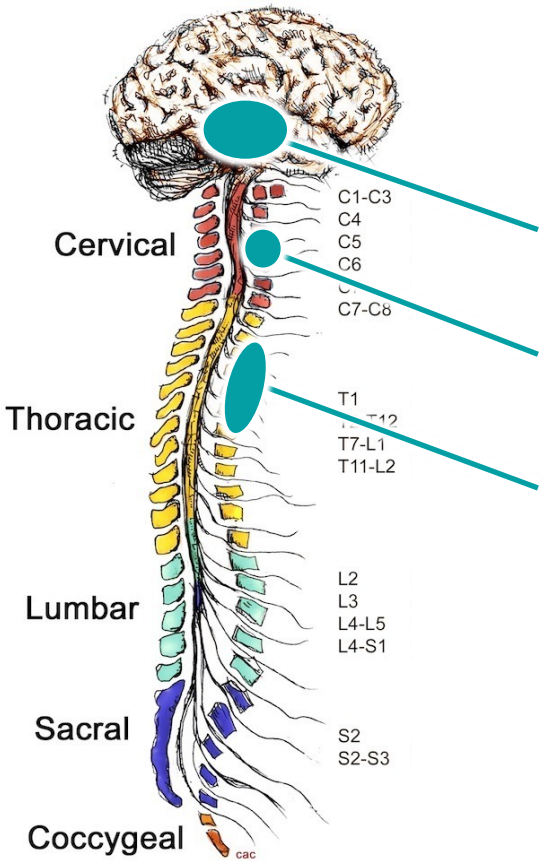
- Tail docking neuroma in piglets

| Variables | Intact tails | Docked tails | *P*-value |
|---|---|---|---|
| Number of animals | 18 | 47 | |
| % of tails with neuromas | 0 | 64 | $P < 0.001$ |
| Number of neuromas per tail | 0 | $1.0 \pm 0.2$ | $P < 0.001$ |
| Mean size of neuromas (μm) | 0 | $1023 \pm 592$ | $P < 0.001$ |

| Variables | 75% left | 50% left | 25% left | s.d. | *P*-value |
|---|---|---|---|---|---|
| Number of animals | $n = 17$ | $n = 19$ | $n = 11$ | | |
| % of tails with neuromas | 53 | 74 | 64 | | ns |
| Number of neuromas per tail | 0.8 | 1.3 | 1.0 | 1.1 | ns |
| Mean size of neuromas (μm) | 797 | 1119 | 1080 | 592 | ns |

# Neuropathic Itch – Radiculopathy

*Disturbances* at the *somatosensory system*




- **Focal NI syndrome**

1. Trigeminal trophic syndrome (*CN V*)
2. Brachioradial pruritus (*C5-C6*)
3. Notalgia paresthetica (*T2-T6*)

Steinhoff. 2018. *Lancet Neurol*

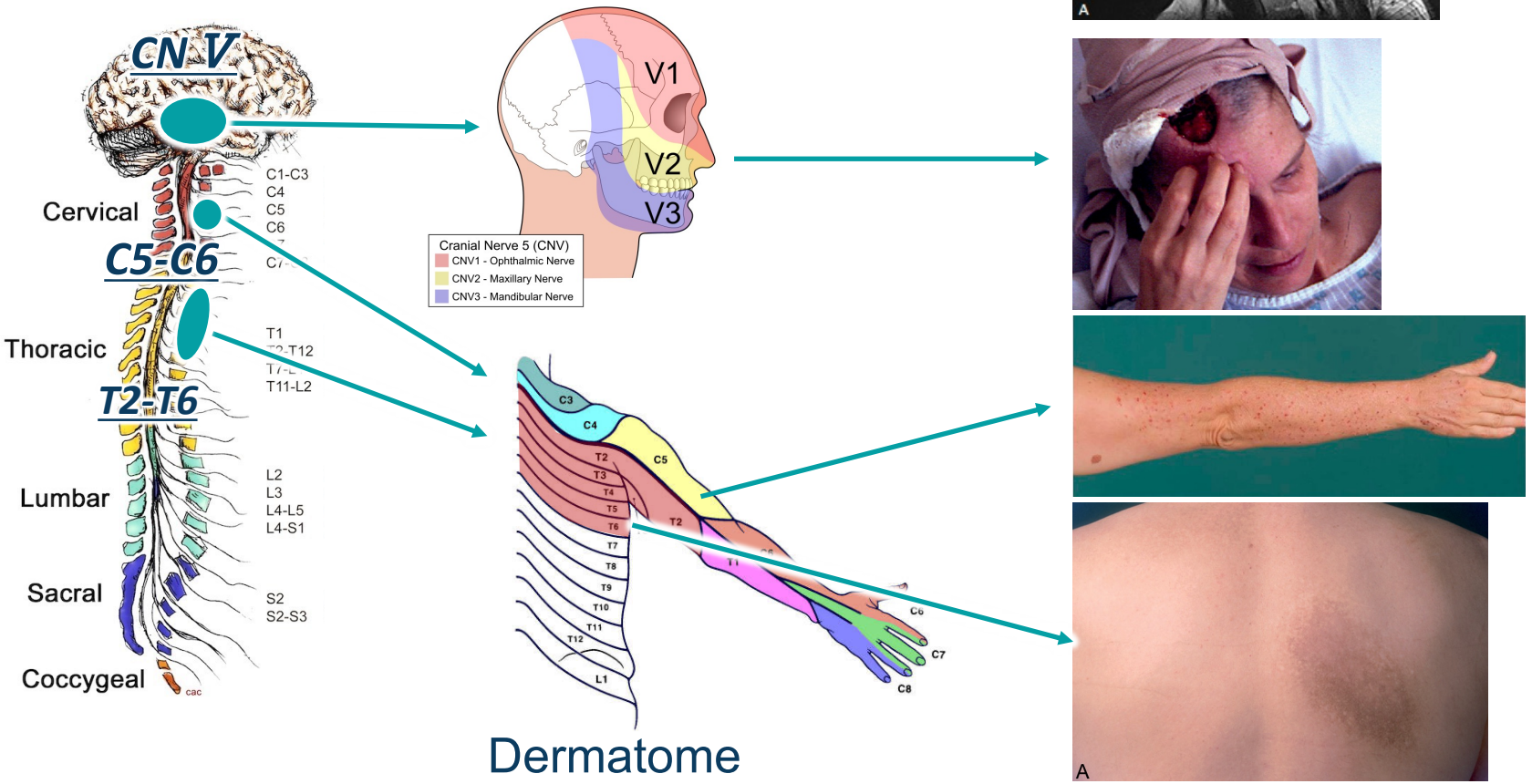
# Neuropathic Itch – Radiculopathy

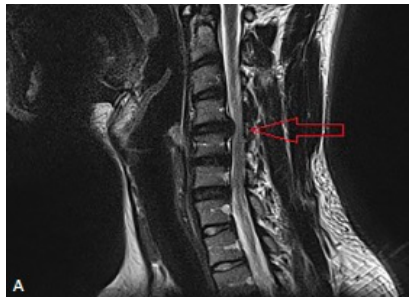
- Diagnostic imaging (CT, MRI)
- Clinical manifestation

Trigeminal trophic syndrome

Brachioradial pruritus

Notalgia paresthetica











Steinhoff. 2018. *Lancet Neurol*

# Neuropathic Itch – Radiculopathy

- 7 years old
- Castrated male
- Labrador retriever

*Chief complaint*

One-month history of **severe localized itch**, unresponsive to glucocorticoid treatment

# History

- No prior history of major skin issues
- Self-grooming facility

  ⬇ 2 days later

- *Severe localized itch*
  - Treatment at rDVM
    - Topical/systemic GC
    - Trazodone
    - Oclacitinib

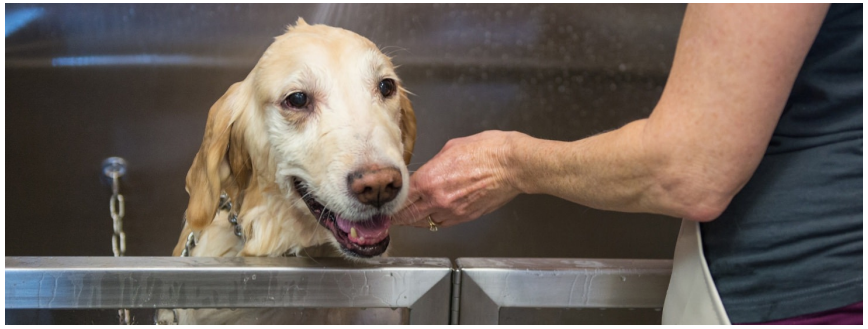
    ➡ No response

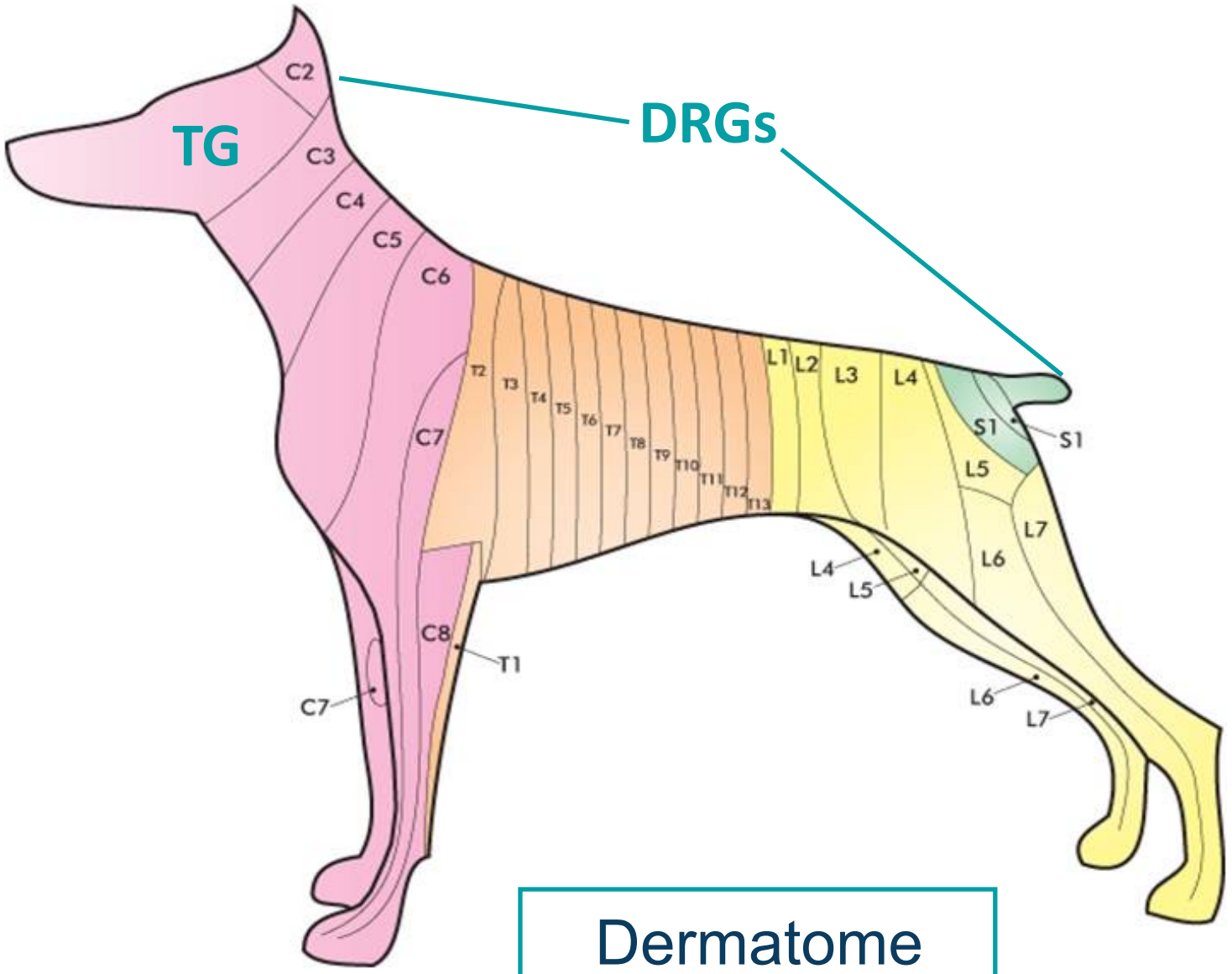
    - Gabapentin (20 mg/kg/d)

    ➡ Slight improvement

    ⬇

    To NCSU



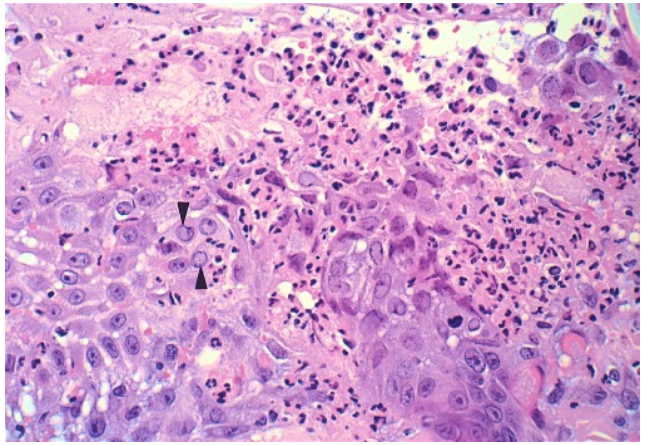

TG
DRGs
C2
C3
C4
C5
C6
C7
C8
T1
T2
T3
T4
T5
T6
T7
T8
T9
T10
T11
T12
T13
L1
L2
L3
L4
L5
L6
L7
S1
S1
L4
L5
L6
L7
C7

Dermatome


# Neuropathic Itch

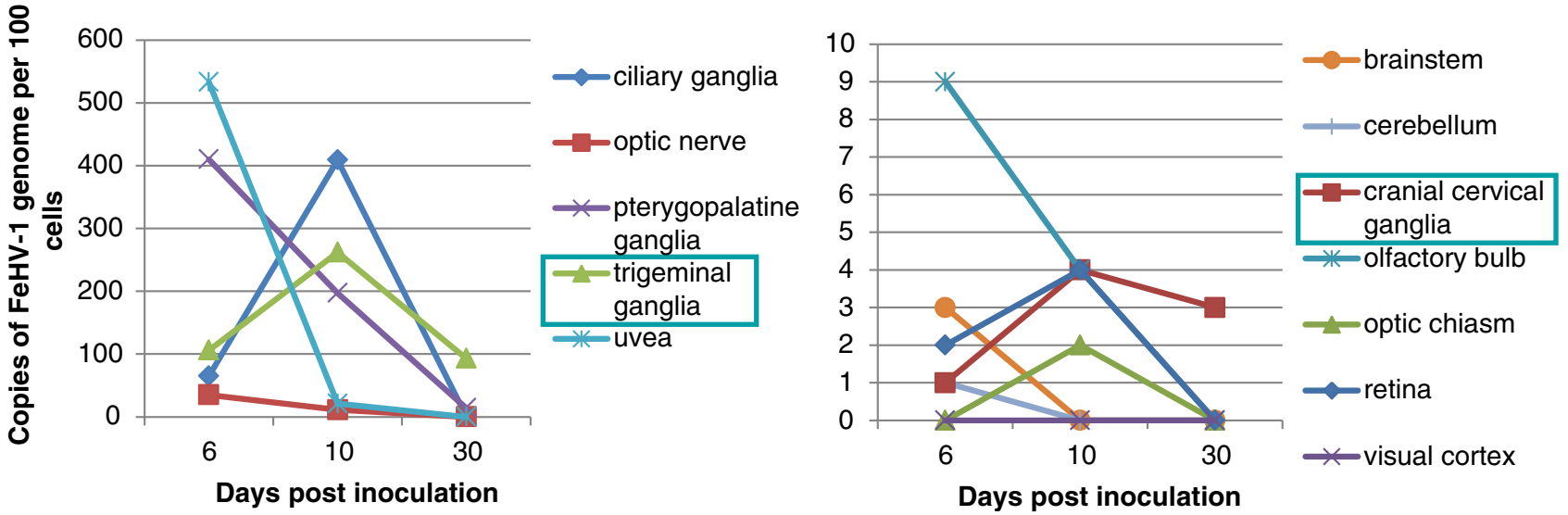
(due to cervical radiculopathy: *C3*)

# Neurogenic/Neuropathic Itch? – FeHV-Associated Dermatitis



- **Facial pruritus**
- Causes - combination of neurogenic (inflammatory) and neuropathic? itch

FeHV-1 experimental infection in cats



# Psychogenic Pruritus

# Psychogenic Itch – Acral Lick Dermatitis (ALD)

- Causes - 1. Allergy 2. Orthopedic 3. Neurologic 4. Neoplasia 5. Focal infection 5. Behavioral

**For behavioral ALD**

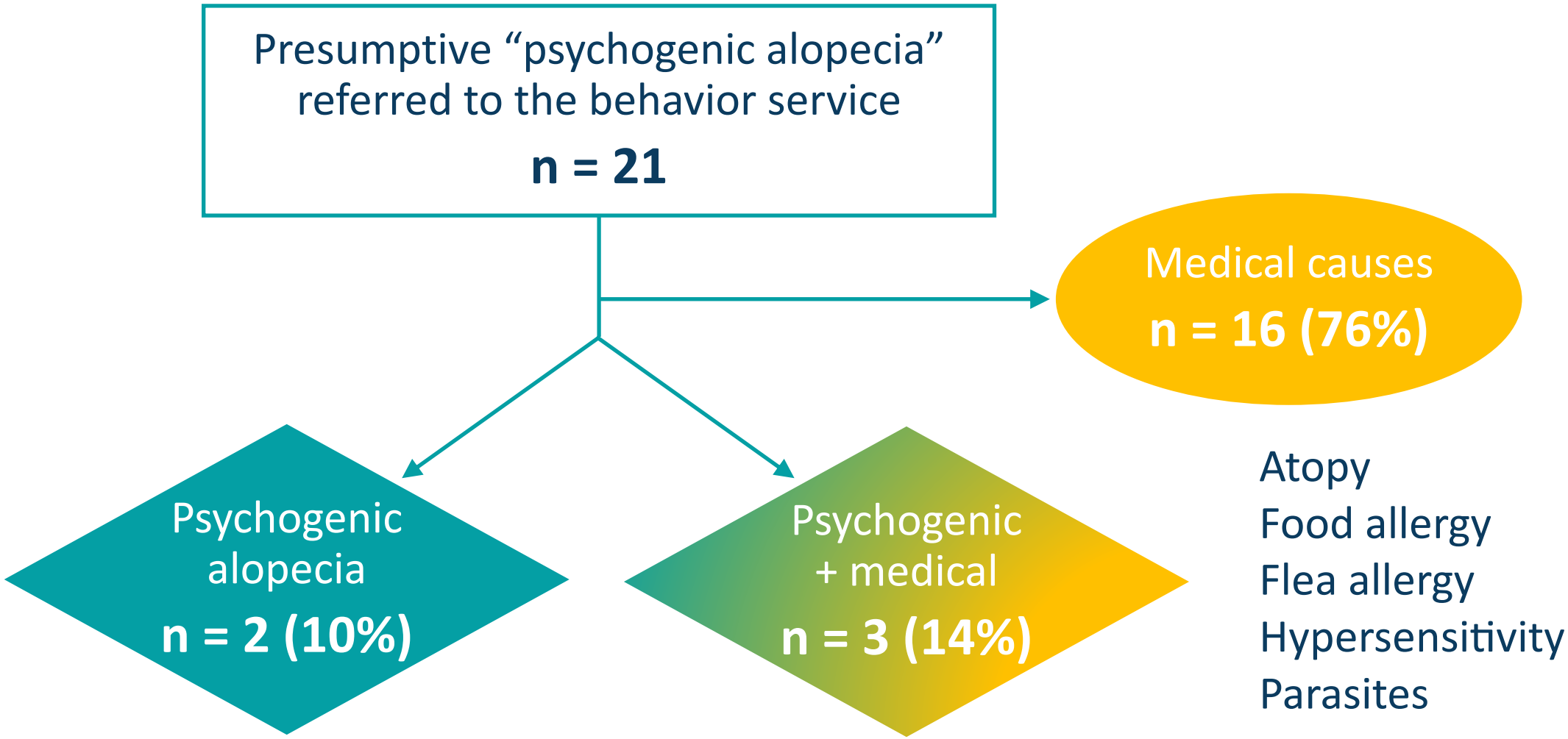
- Prevalence - 50% of ALD??
- Breeds - Large breeds (Doberman pinscher, Great Dane, Labrador retriever, Irish setter, golden retriever, boxer, Weimaraner, German shepherd)
- Median age - 4 years old
- Diagnosis - by exclusion

Shumaker. 2019. *Vet Clin Small Anim*

# Psychogenic Itch – Feline Psychogenic Alopecia

- Causes - stress-related overgrooming
- Prevalence - 1.2 - 4.7% of itchy cats
- Breeds - Siamese, Abyssinian, Asian cats??
- Age - no predilections
- Diagnosis - by exclusion

# Psychogenic Itch – Feline Psychogenic Alopecia



# Psychogenic Itch? – Feline Idiopathic Ulceration

- Causes - unknown
  - *self-induced by stress??*
- Clinical presentation
  - non-healing ulceration at dorsal neck and shoulder
- Diagnosis - by exclusion

CR: all 15 cats

Day 15

Modification of cat environment
No medication

# Quiz!

**5. What is the name of gene that is associated with acral mutilation dermatitis in German short-haired pointer?**

| | | |
|---|---|---|
| a. | PNPLA1 | Ichthyosis |
| d. | GDNF | Acral mutilation syndrome |
| c. | FLCN | Nodular dermatofibrosis |
| d. | HAS2 | Shar-Pei fever |

# 4. Management of Neuropathic Itch

# Neuropathic Itch – Treatment

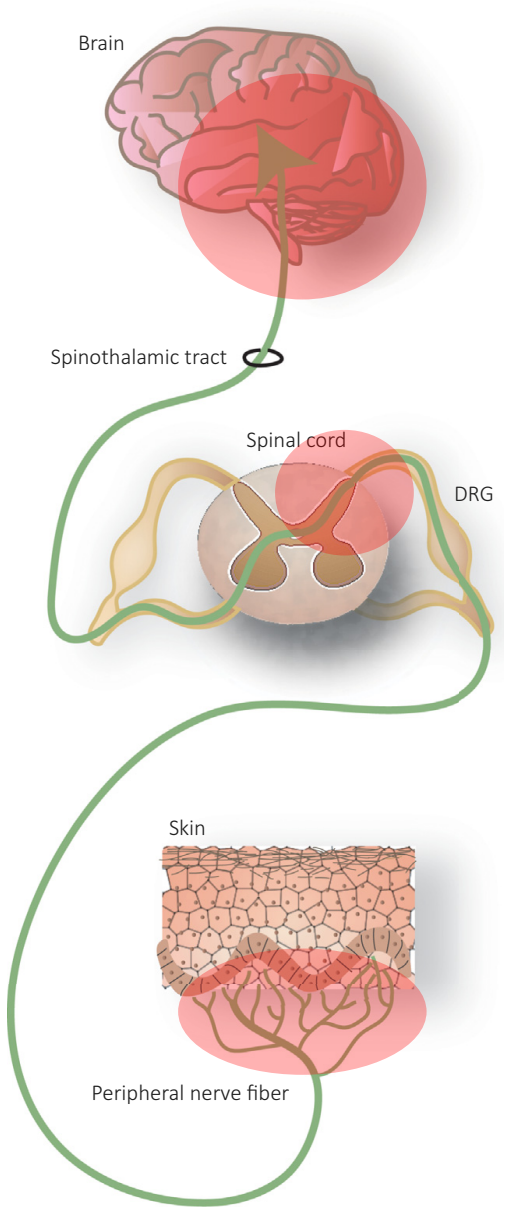
- No therapies for NI have been approved
- Anti-histamine, glucocorticoids, pain medications

  ➡ ineffective…

- Recommendations:
  - Barriers to reduce scratching
  - Local anesthetics

Steinhoff. 2018. *Lancet Neurol*

# Choice of medications depending on the target level of the nerve system




- TCAs
- SSRIs, SNRIs
- Mirtazapine
- Gabapentin, Pregabalin
- Kappa-opioid agonists
- NK-1R inhibitors

- Gabapentin, Pregabalin
- Kappa-opioid agonists
- NK-1R inhibitors

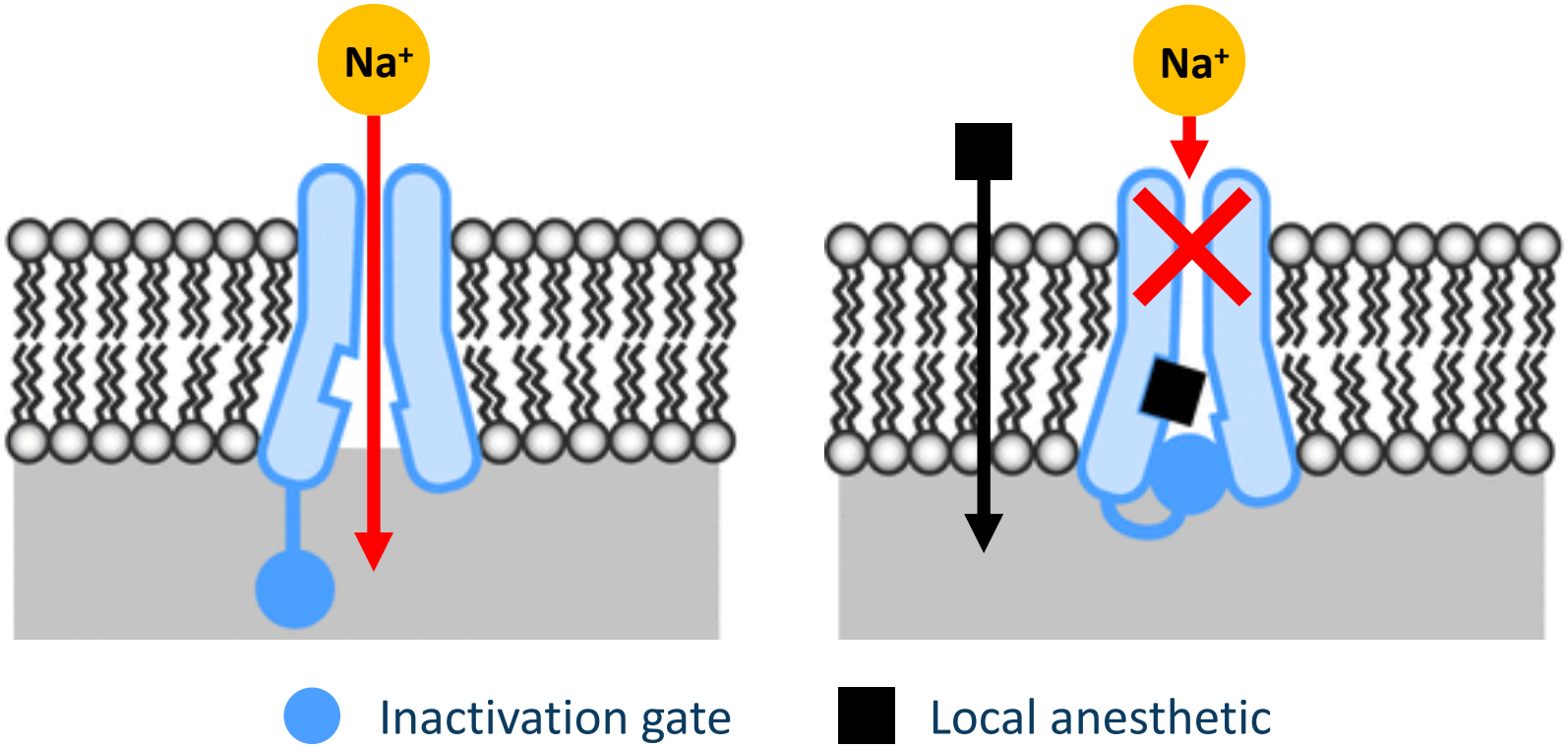
- Topical anesthetics
- Topical capsaicin
- Topical menthol
- Topical cannabinoids
- Anti-histamines
- NK-1R inhibitors
- Lokivetmab

Folwer 2019. *Ann Allergy Asthma Immunol*

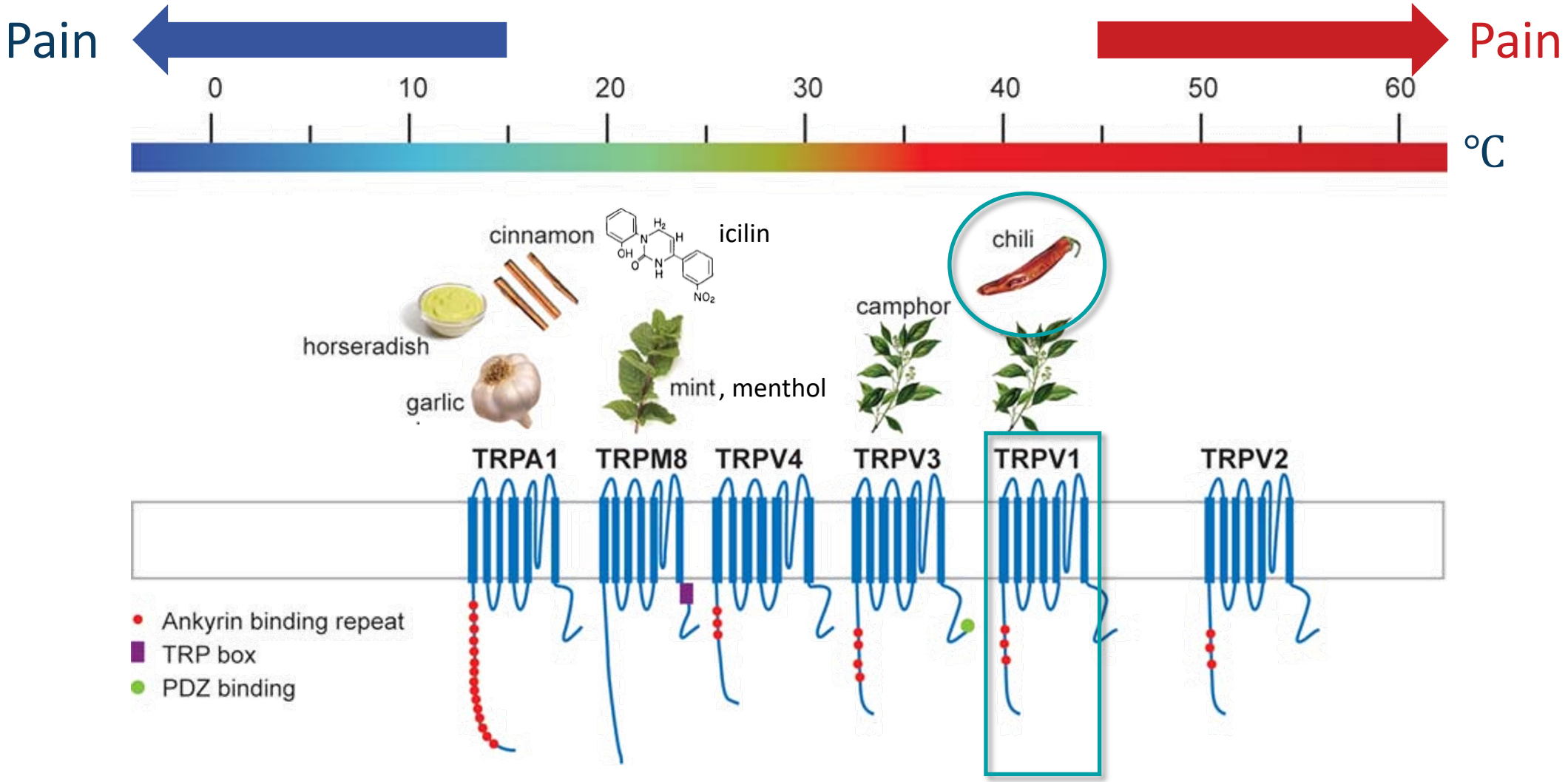
# PNS – Topical Anesthetics

- Lidocaine
- Prilocaine
- Pramoxine


<u>*Nerves*</u>



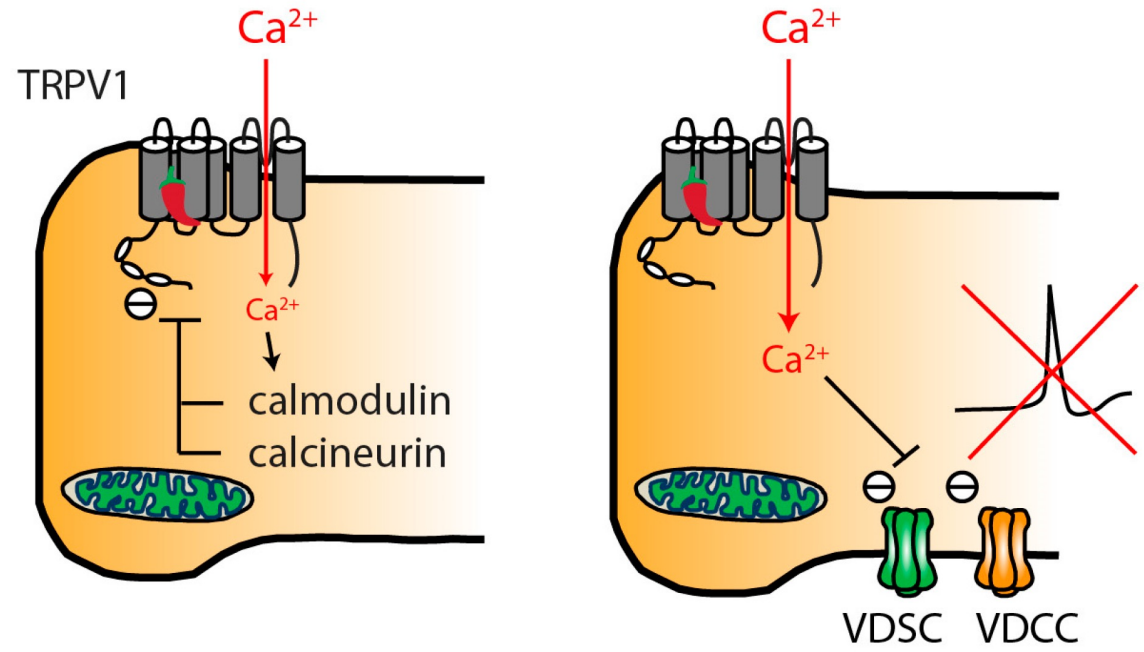
# PNS – Topical Capsaicin




Dhaka. 2006. *Annu. Rev Neurosci*

# PNS – Topical Capsaicin

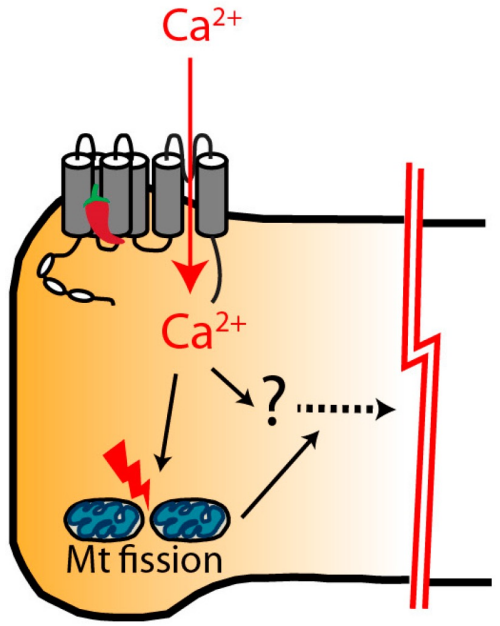
## *Transient analgesia*




**Desensitization of TRPV1**
(decreased function of TRPV1)

**Functional inhibition of axonal terminals**
(inhibition of action potential firings)

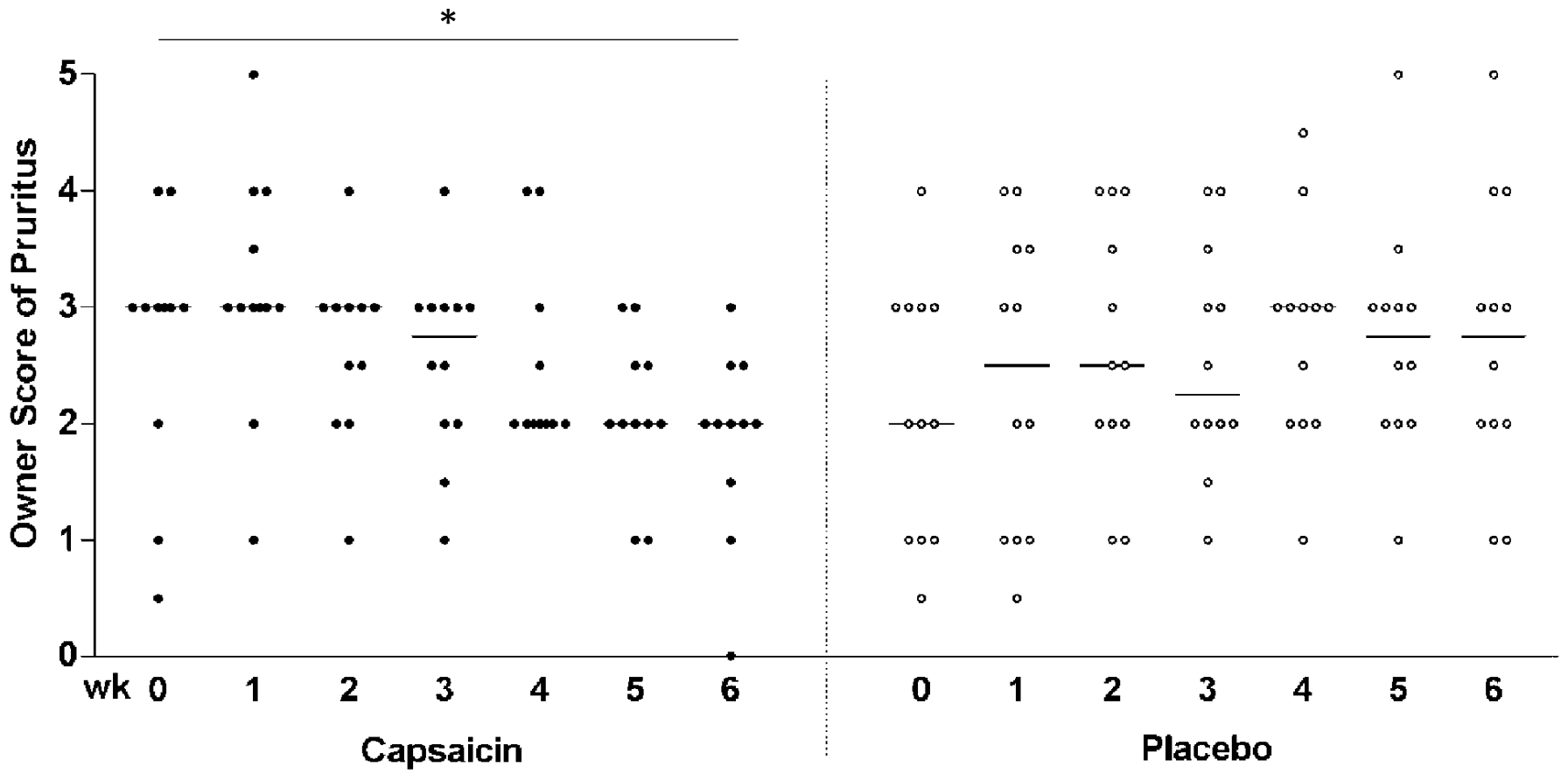
## *Long-acting effect*




**Structural changes of axonal termianls**
(ablation of axonal terminals)

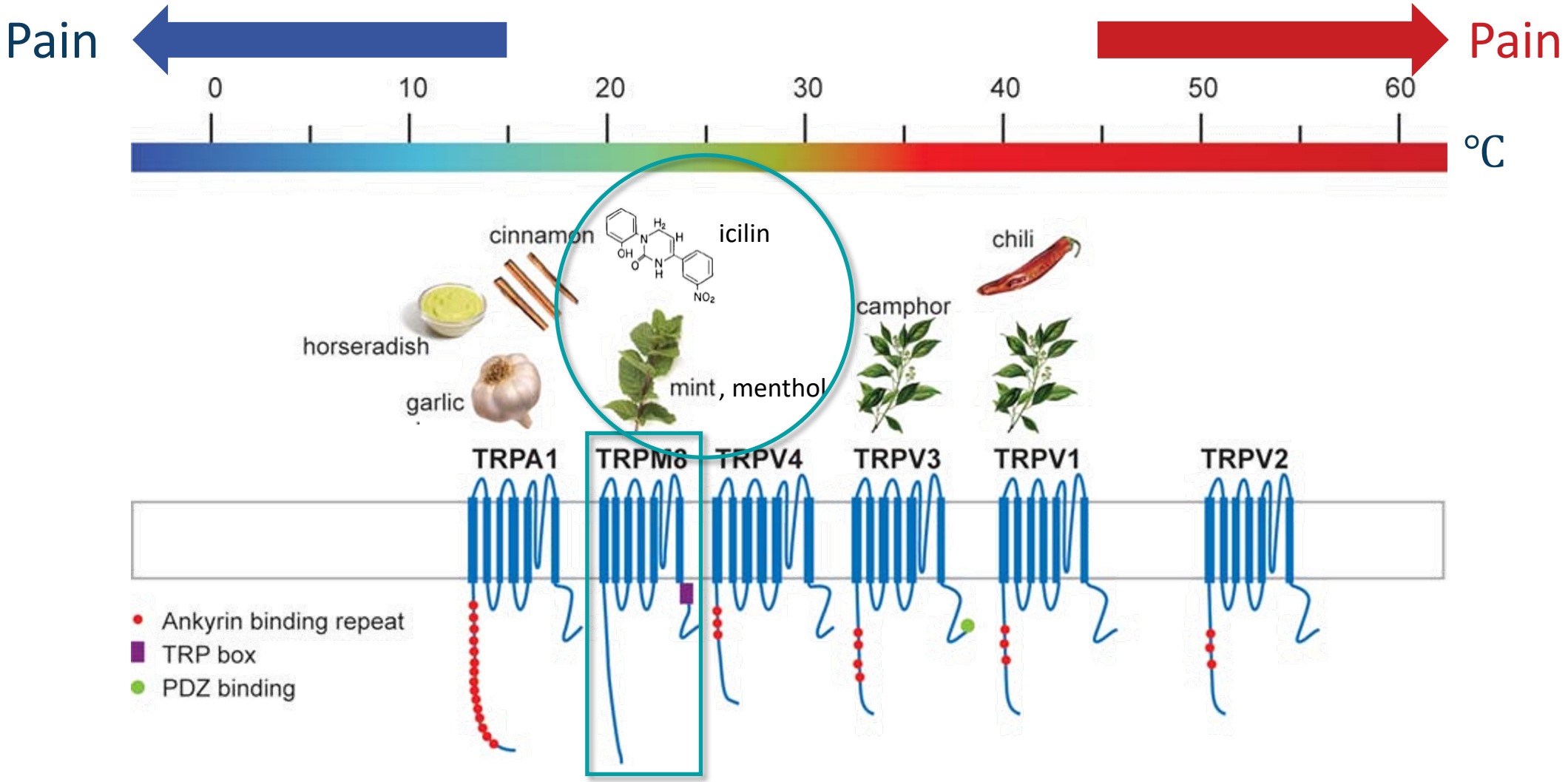
# PNS – Topical Capsaicin

- 12 AD dogs
- 0.025% topical capsaicin, q12h, for 6 weeks



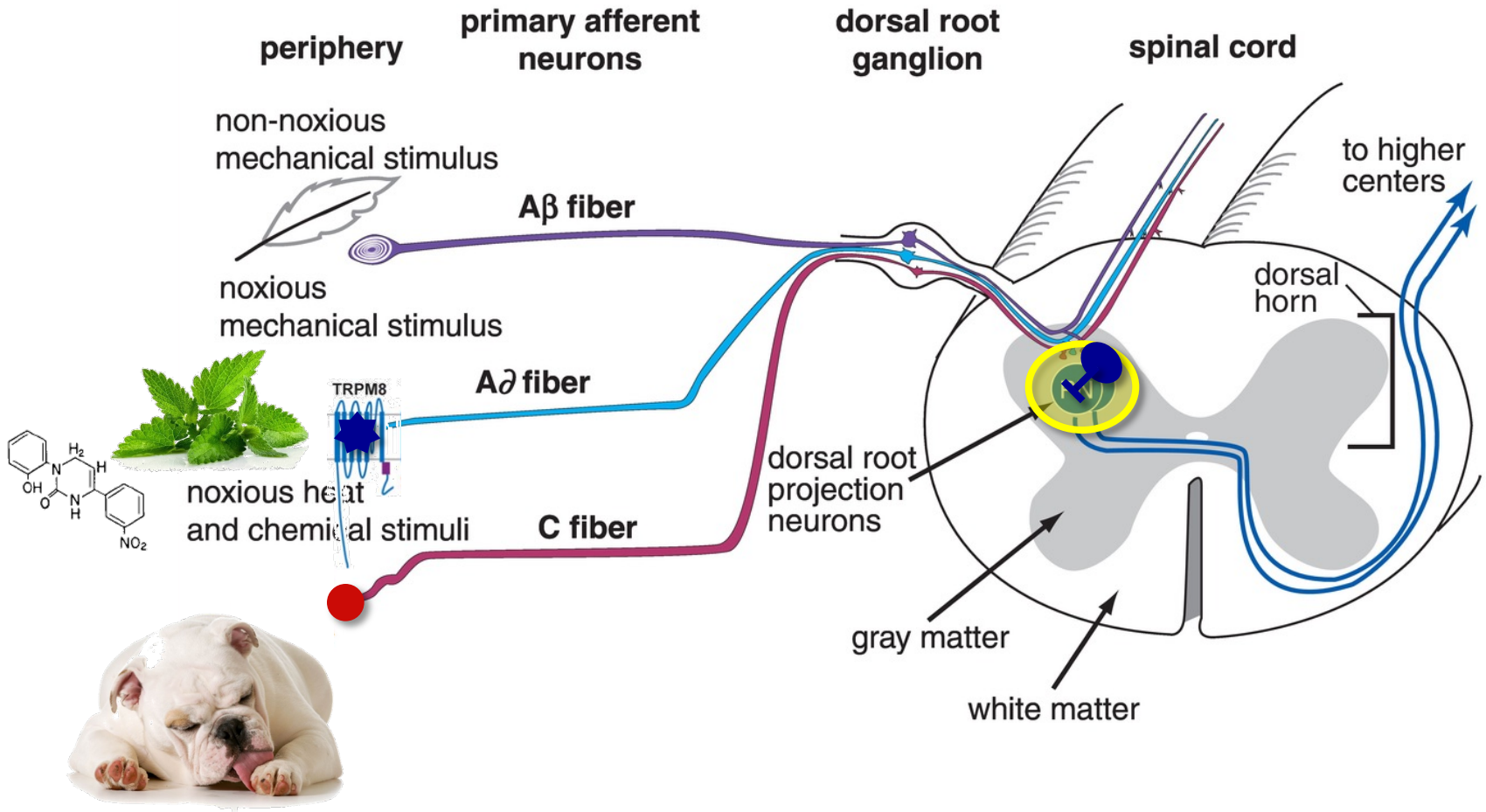

Marsella. 2002. *Vet Dermatol*

# PNS – Topical TRPM8 Agonist




Dhaka. 2006. *Annu. Rev Neurosci*

# PNS – Topical TRPM8 Agonist

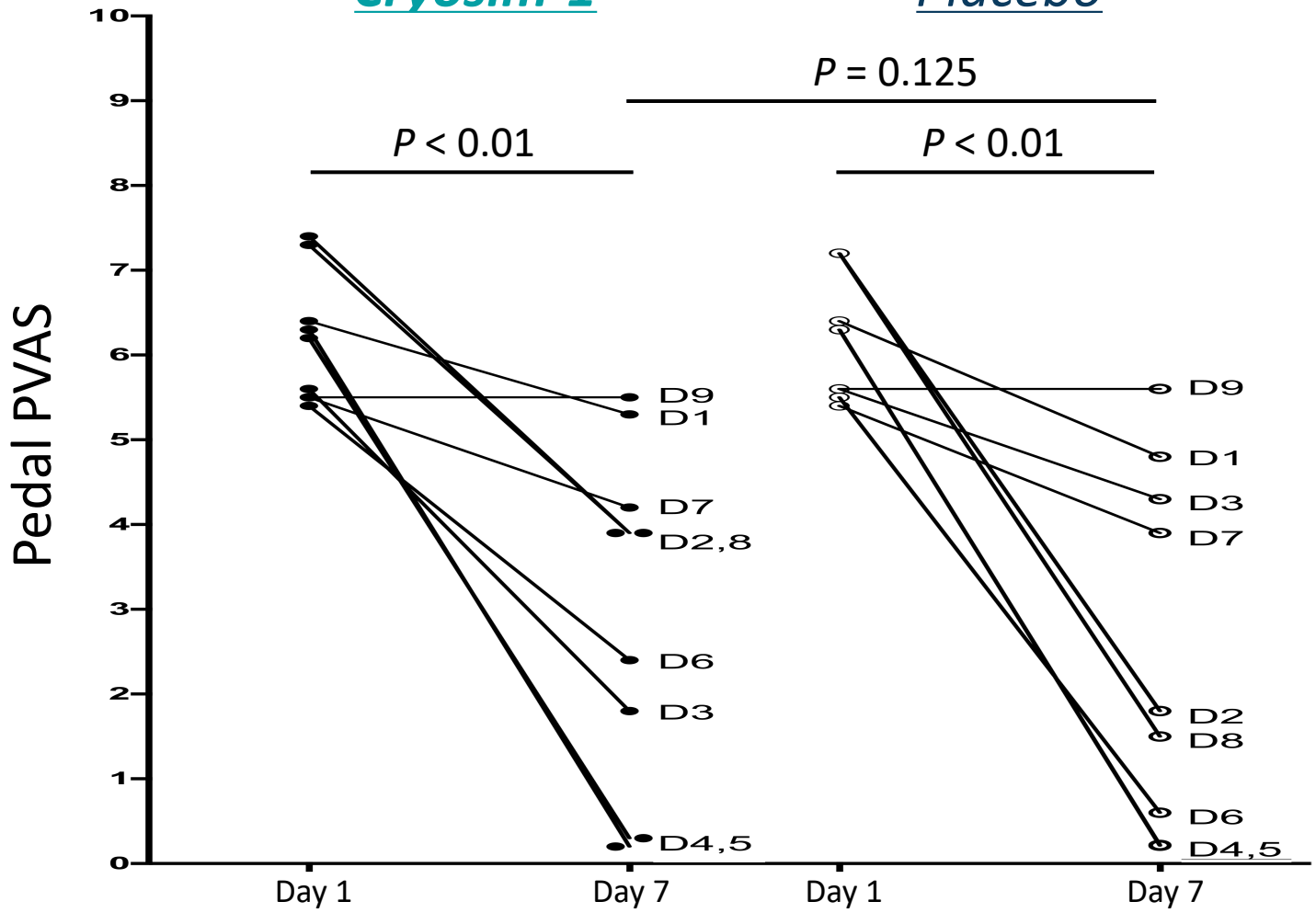



Excitation of Aδ fibers by TRPM8 (cold) inhibits the signaling of C fibers (itch)

# PNS – Topical TRPM8 Agonist

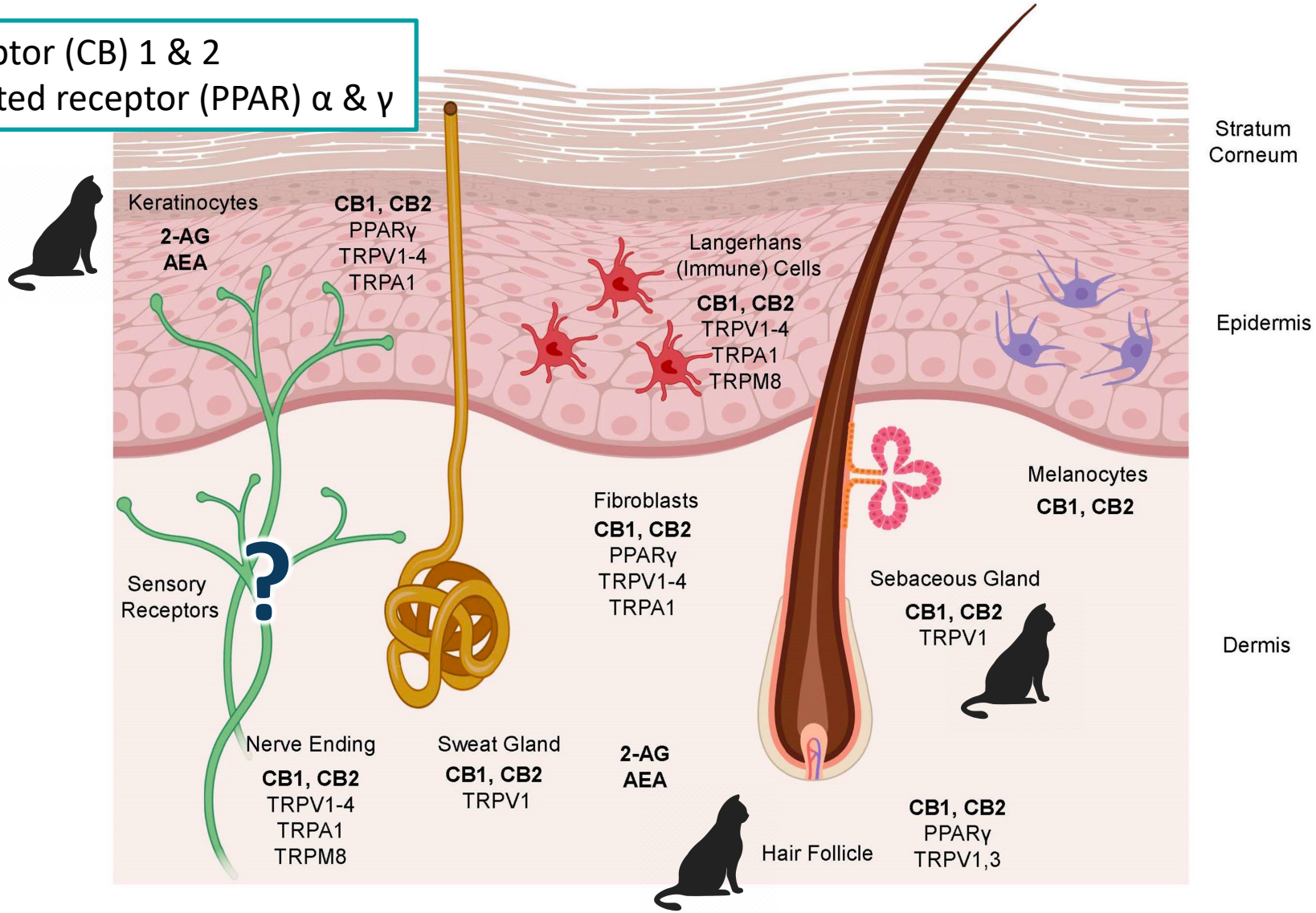
- 9 AD dogs
- 2% topical **cryosin-1** q12h, for 7 days

*No significant difference between two treatment groups*



# PNS & CNS – Cannabinoids

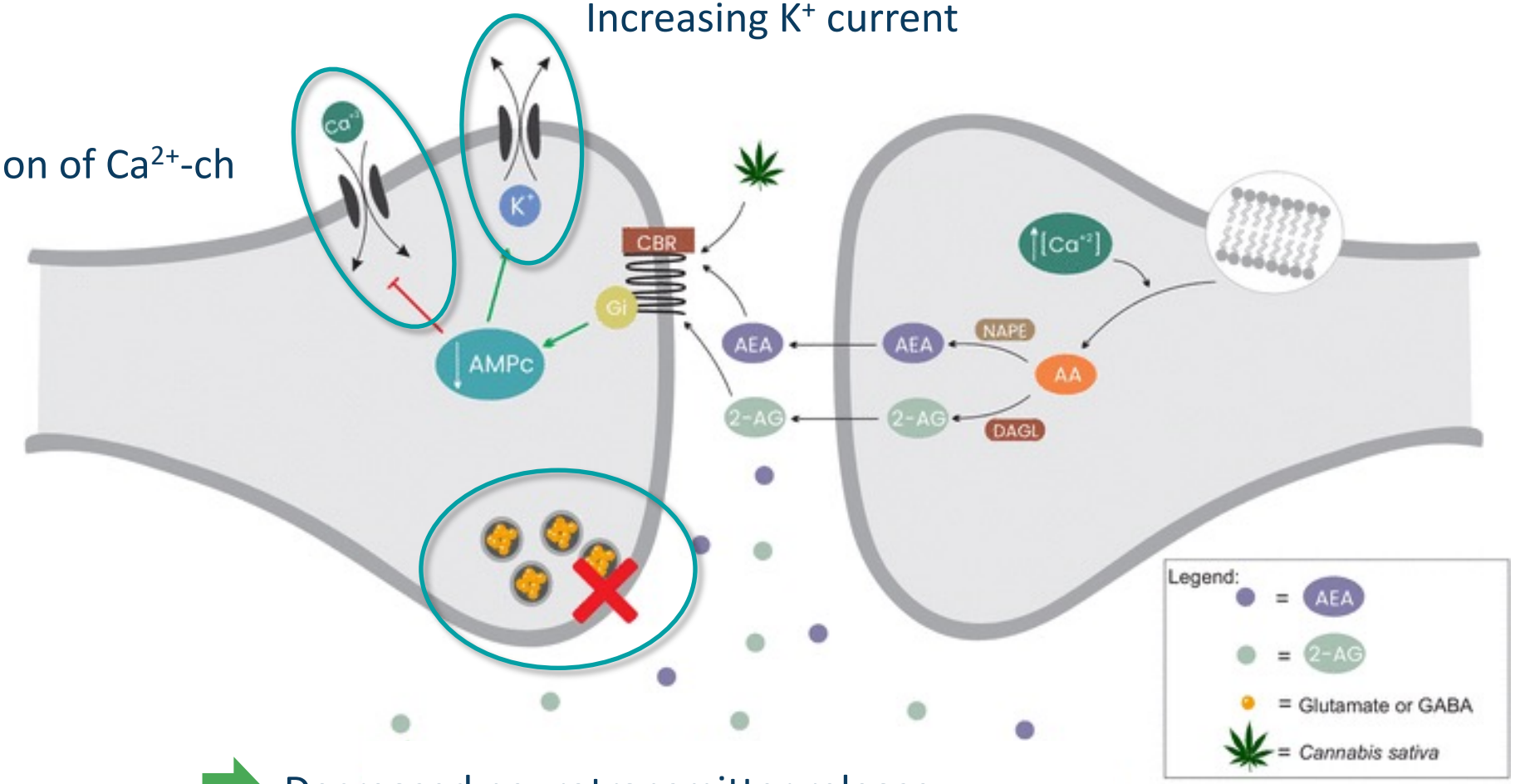
Cannabinoid receptor (CB) 1 & 2
Proliferator-activated receptor (PPAR) α & γ



# PNS & CNS – Cannabinoids

Increasing $K^+$ current

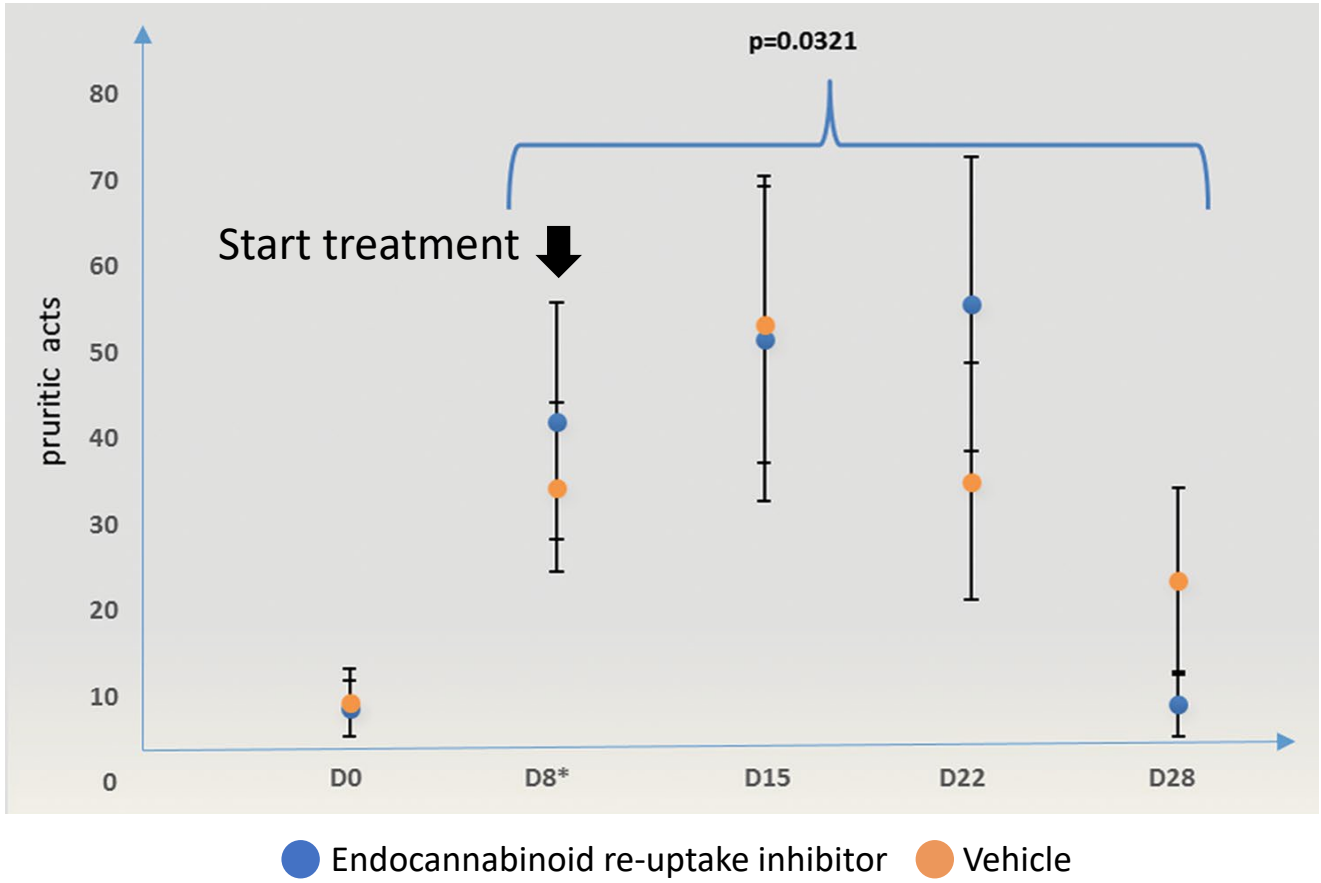
Inhibition of $Ca^{2+}$-ch




➡ Decreased neurotransmitter release

# PNS & CNS – Cannabinoids

- 19 experimental AD dogs
- Topical **endocannabinoid reuptake inhibitor**, q12-24h

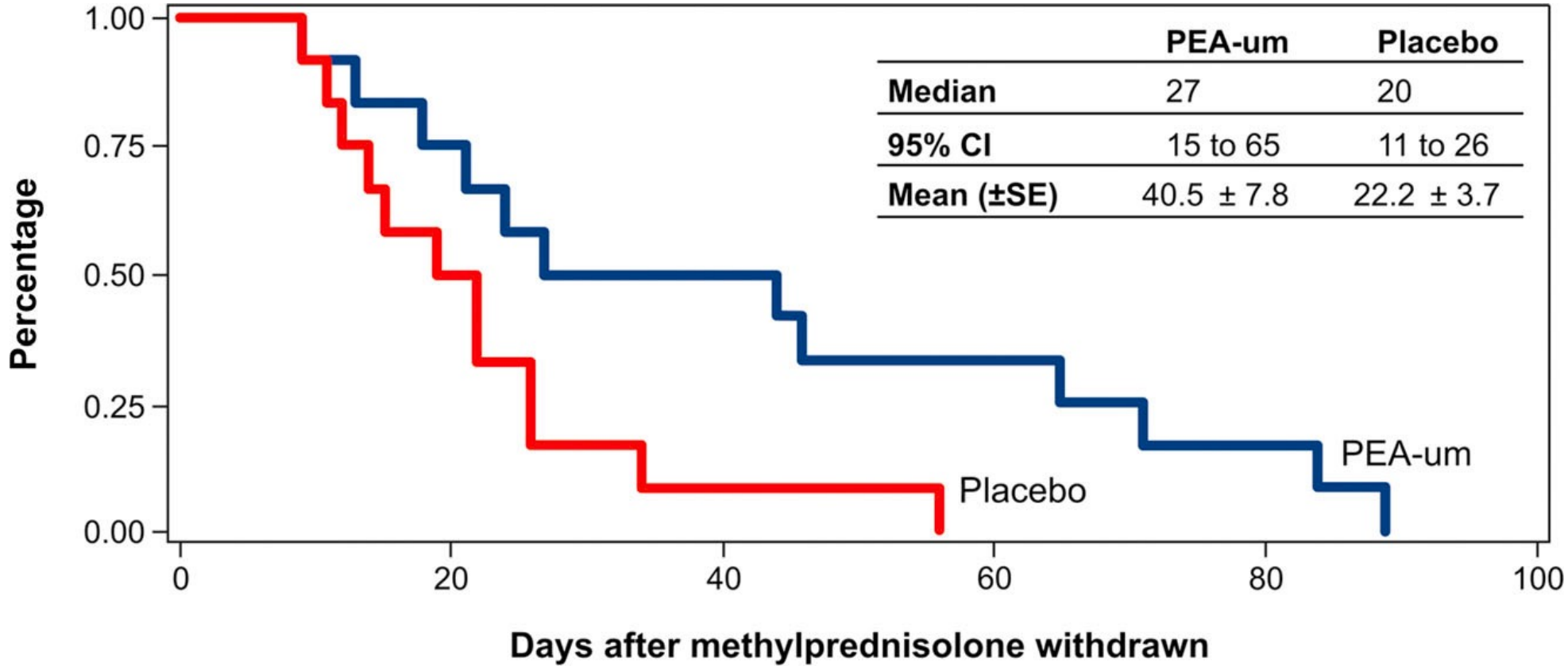



*Inhibitor group*

- Significant reduction of pruritus compared to the baseline (Day 8)
- No difference with placebo

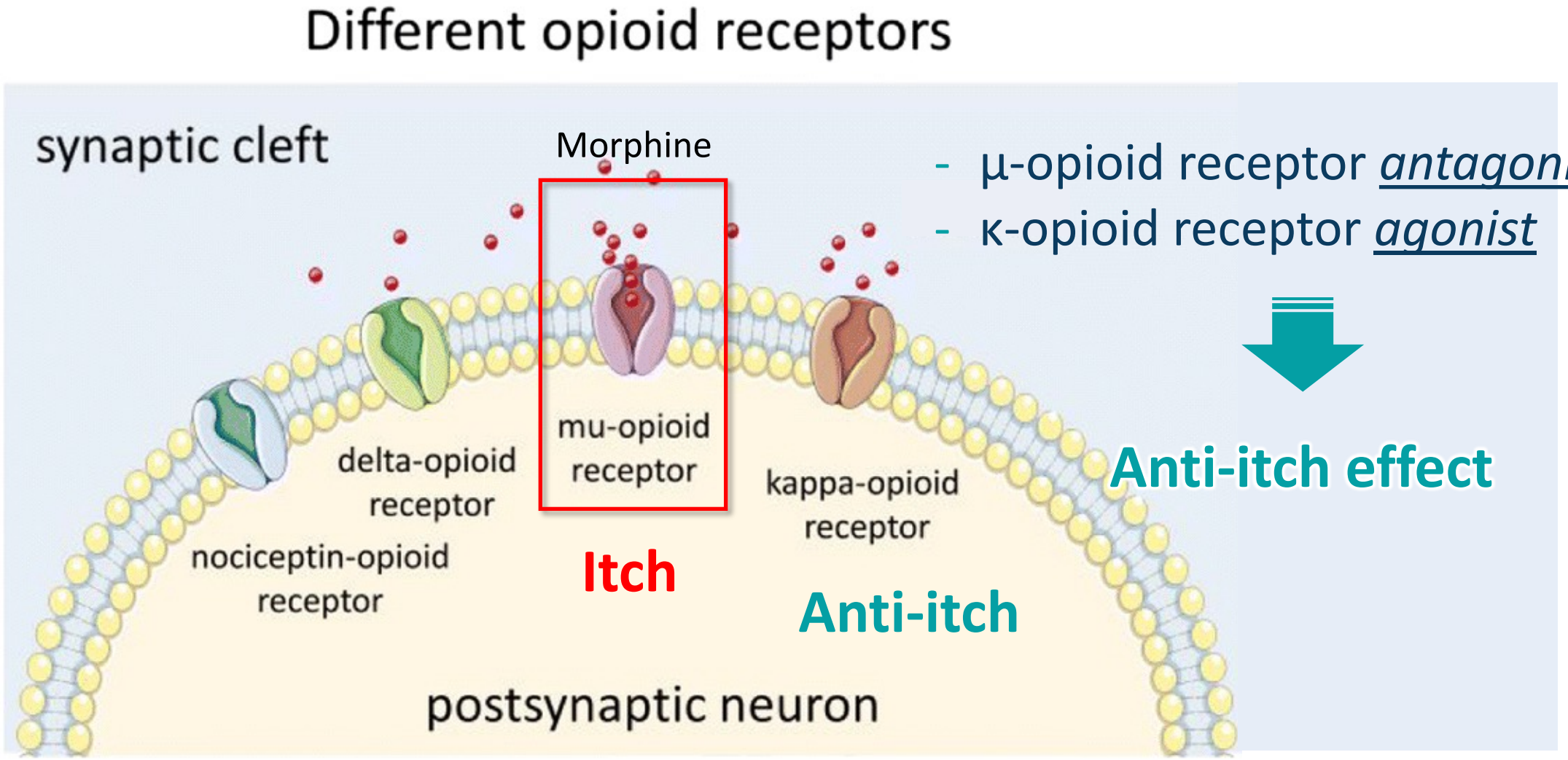
# PNS & CNS – Cannabinoids

- 15 AD cats
- **Ultramicronized Palmitoylethanolamide** (PEA-um), 15 mg/kg q24h




| | PEA-um | Placebo |
|---|---|---|
| **Median** | 27 | 20 |
| **95% CI** | 15 to 65 | 11 to 26 |
| **Mean (±SE)** | 40.5 ± 7.8 | 22.2 ± 3.7 |

# PNS & CNS – Opioid Receptors



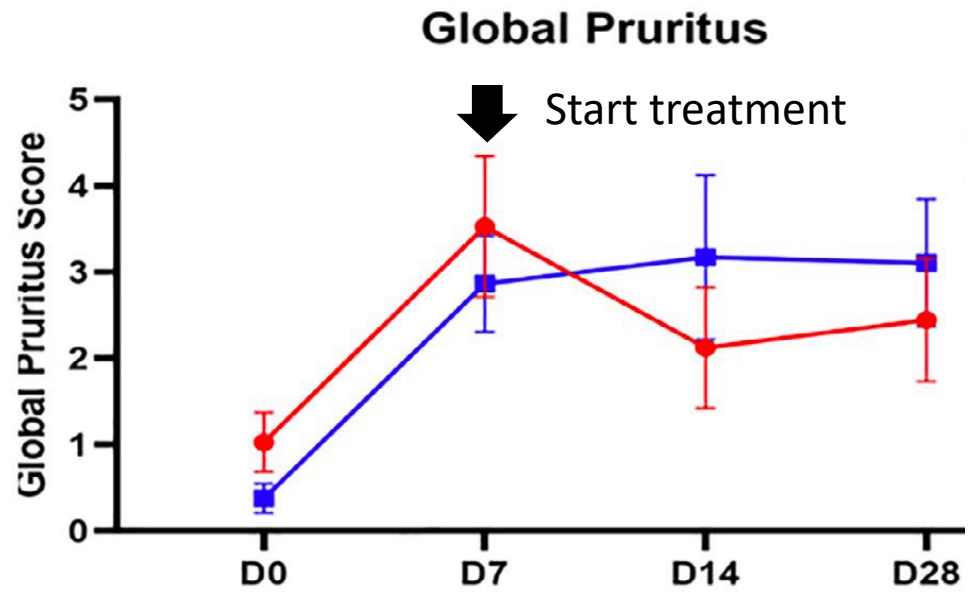

- μ-opioid receptor *antagonist*
- κ-opioid receptor *agonist*

**Anti-itch effect**

# PNS & CNS – Opioid Receptors

- Naltrexone (μ-opioid antagonist)
  - Positive response in acral lick dermatitis

- Asimadoline (κ-opioid agonist)
  - 14 experimental AD dogs
  - 1% topical asimadoline, 4 weeks

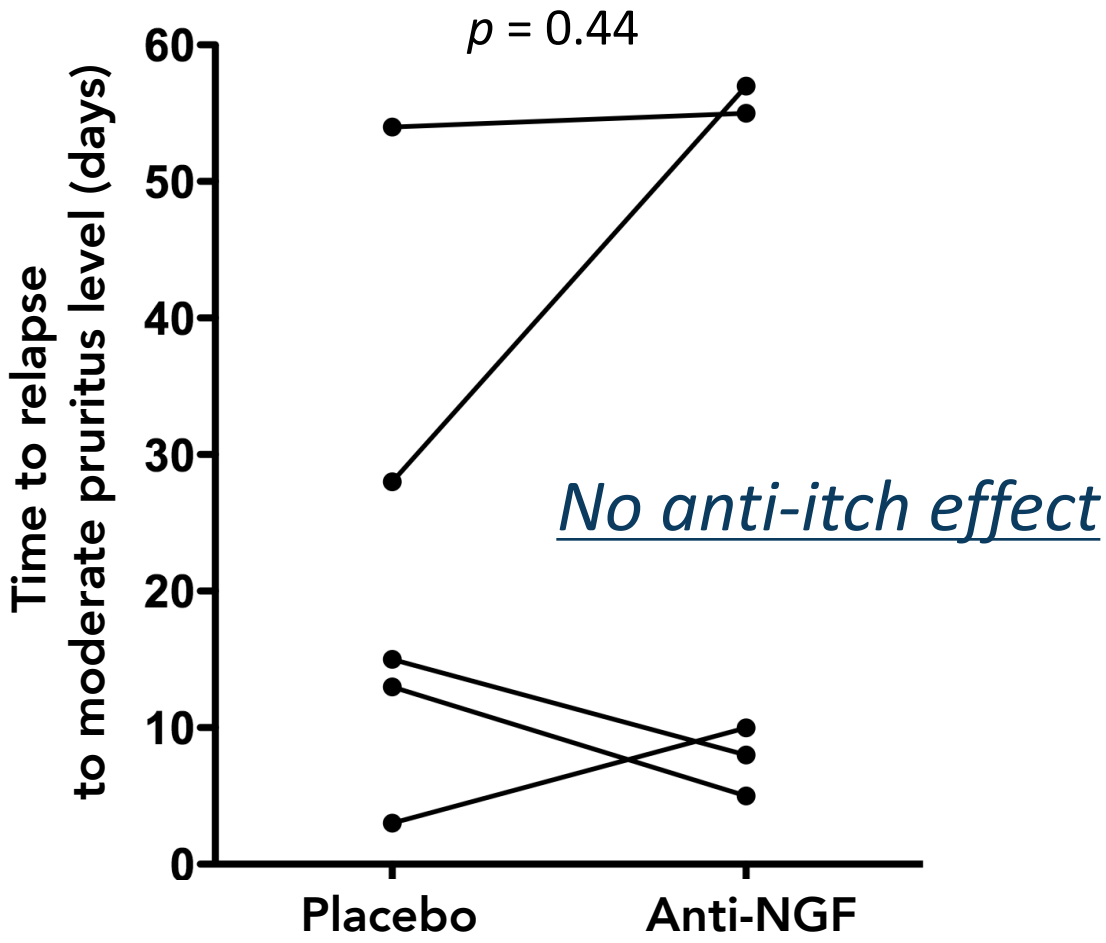



White. 1990. *J Am Med Assoc;* Marsella. 2021. *Exp Dermatol*

# PNS – Anti-NGF mAb

- 5 AD dogs

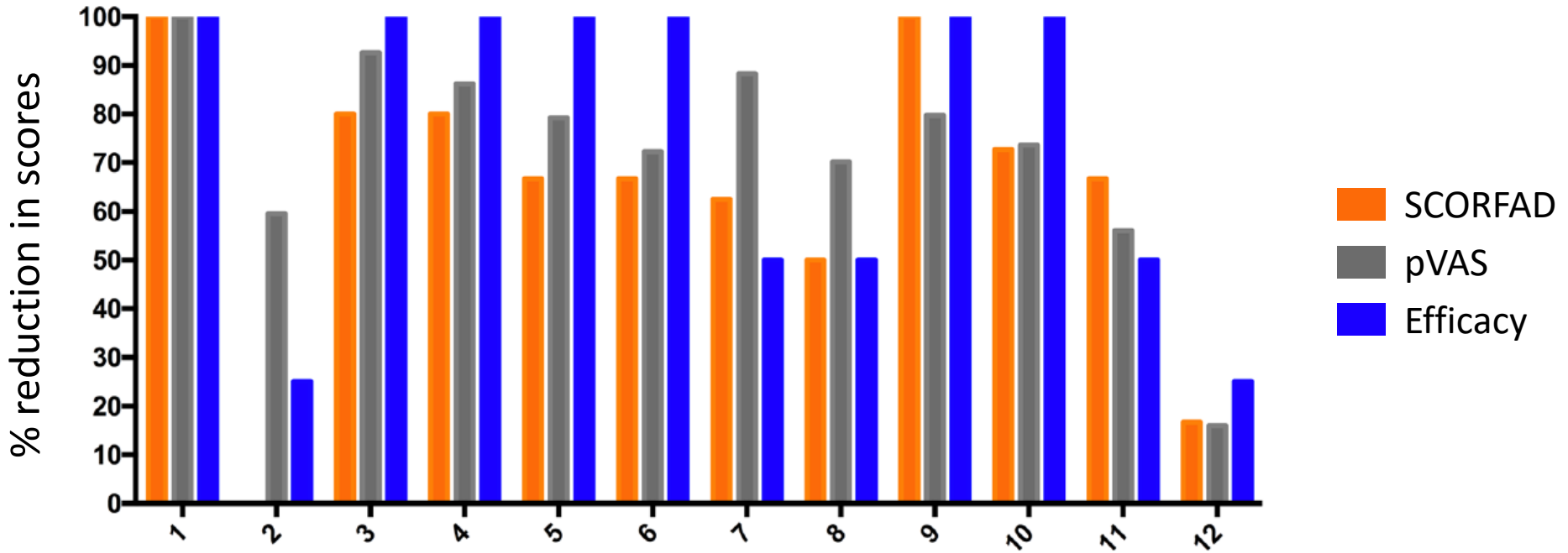

**anti-NGF mAb**
(ranevetmab)




*No anti-itch effect*

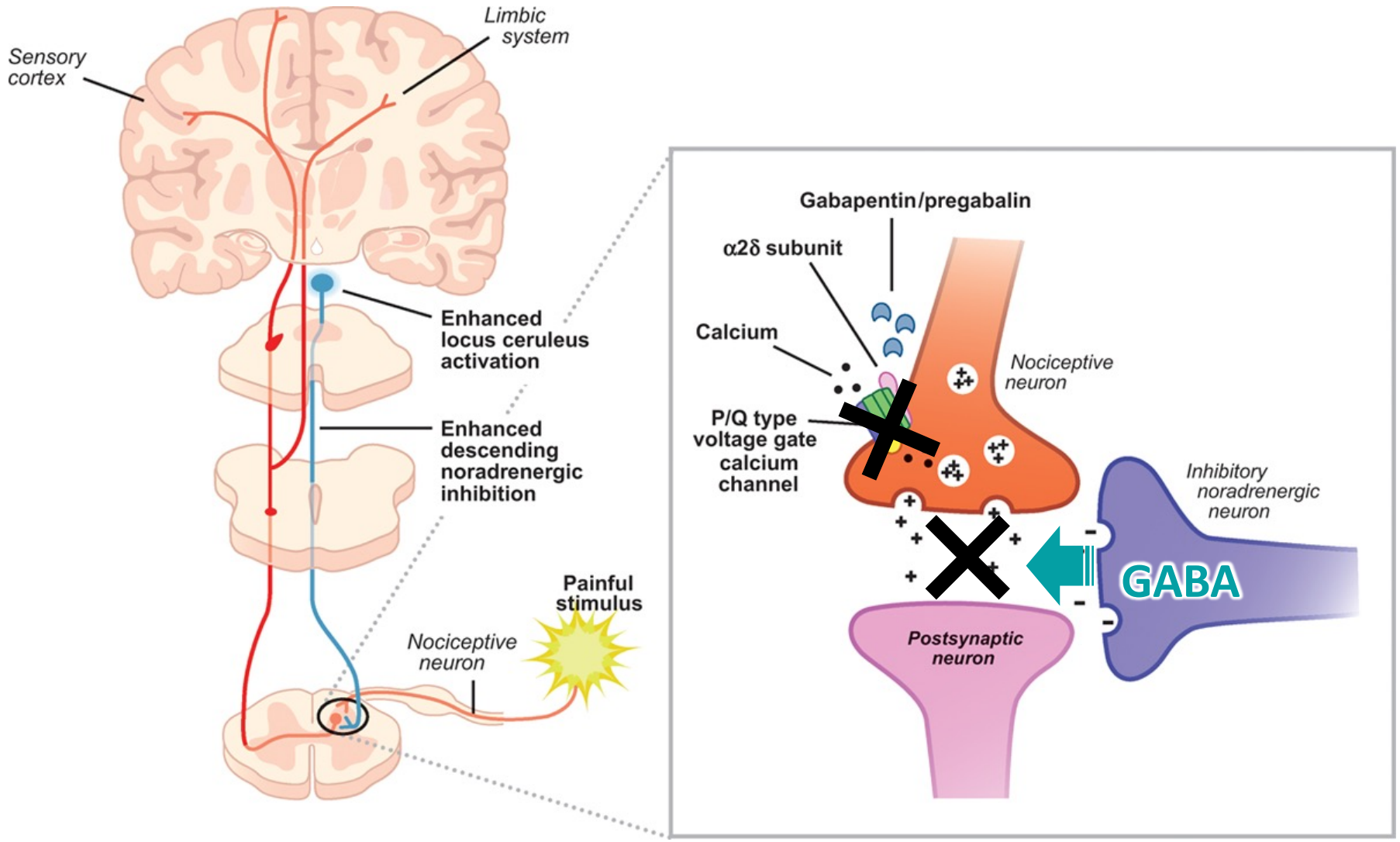
# PNS & CNS – Maropitant (NK-1R inhibitor)

- 12 AD cats (open-labeled, uncontrolled pilot study)
- **Maropitant** 2 mg/kg, q24h for 4 weeks




✓ Might be effective in cats
(but no data in dogs)

# CNS – Gabapentin



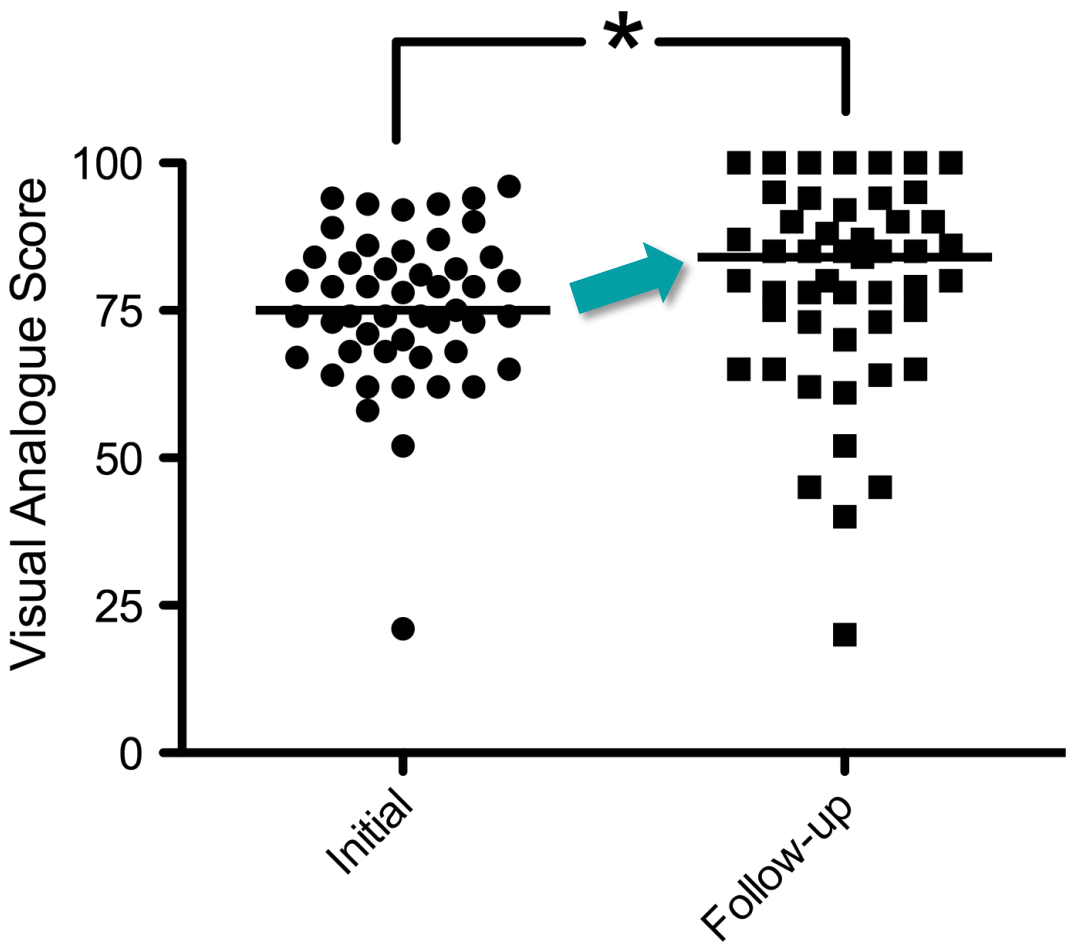

Schimidt. 2013. *Anesthesiology*

# CNS – Gabapentin

- 48 CKCS dogs w/ Chiari-like malformation +/- syringomyelia (retro study)
- **Gabapentin** 10 mg/kg q8-12h or **Pregabalin** (2-4 mg/kg, q8h) +/- carprofen treated (n = 39)

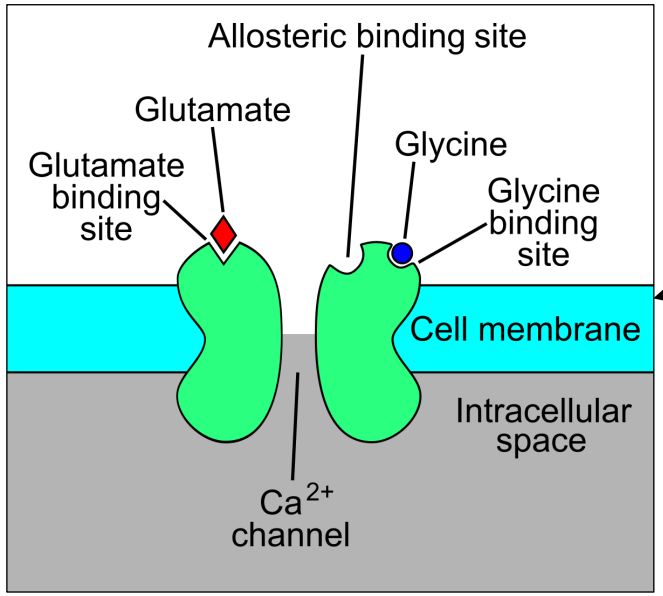
  or no treatment (n = 9)

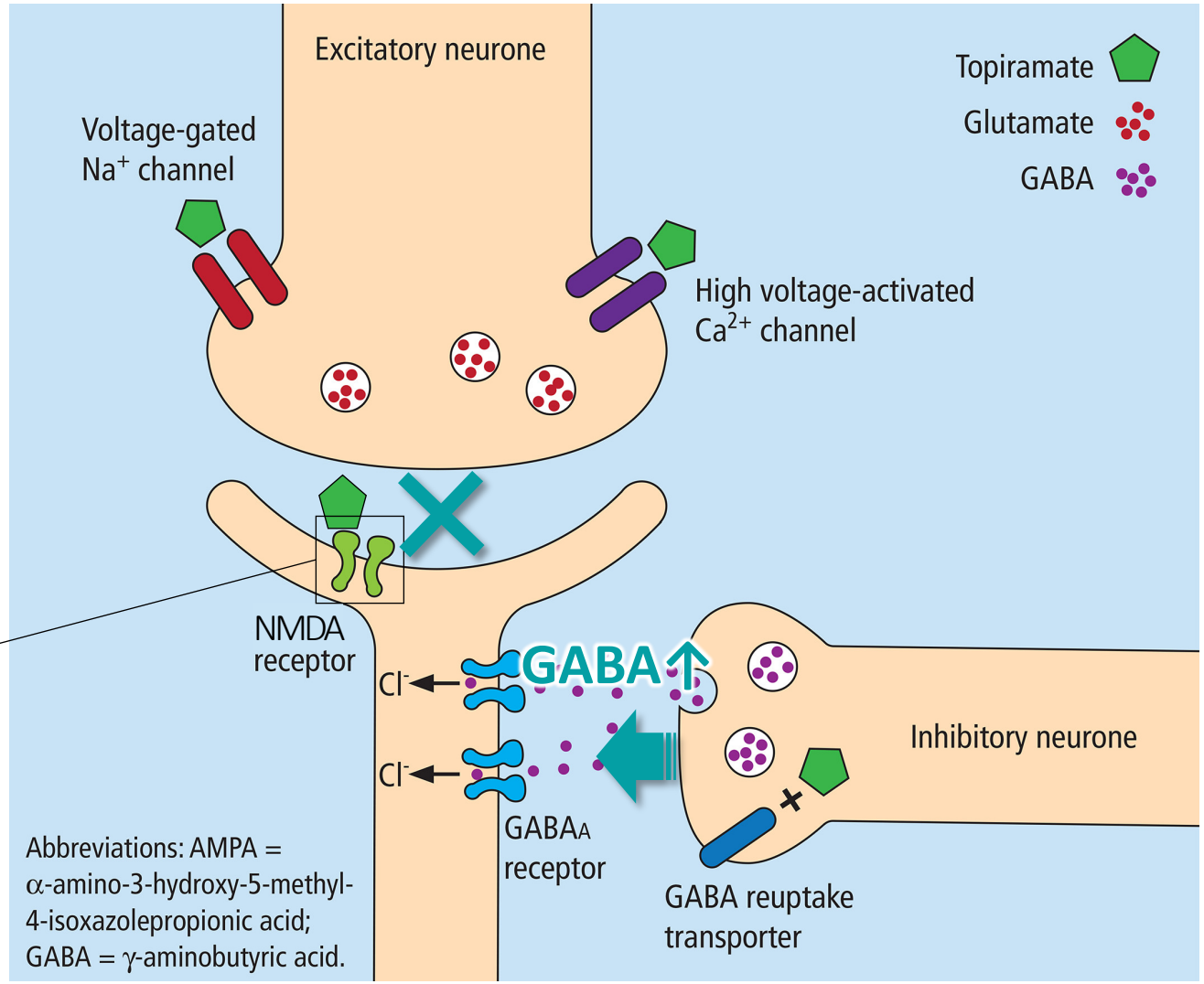
✓ Deterioration of pruritus over time



# Systemic Drug – NMDA Receptor Antagonist

- Amantadine
- Topiramate




*NMDA: N-methyl D-aspartate

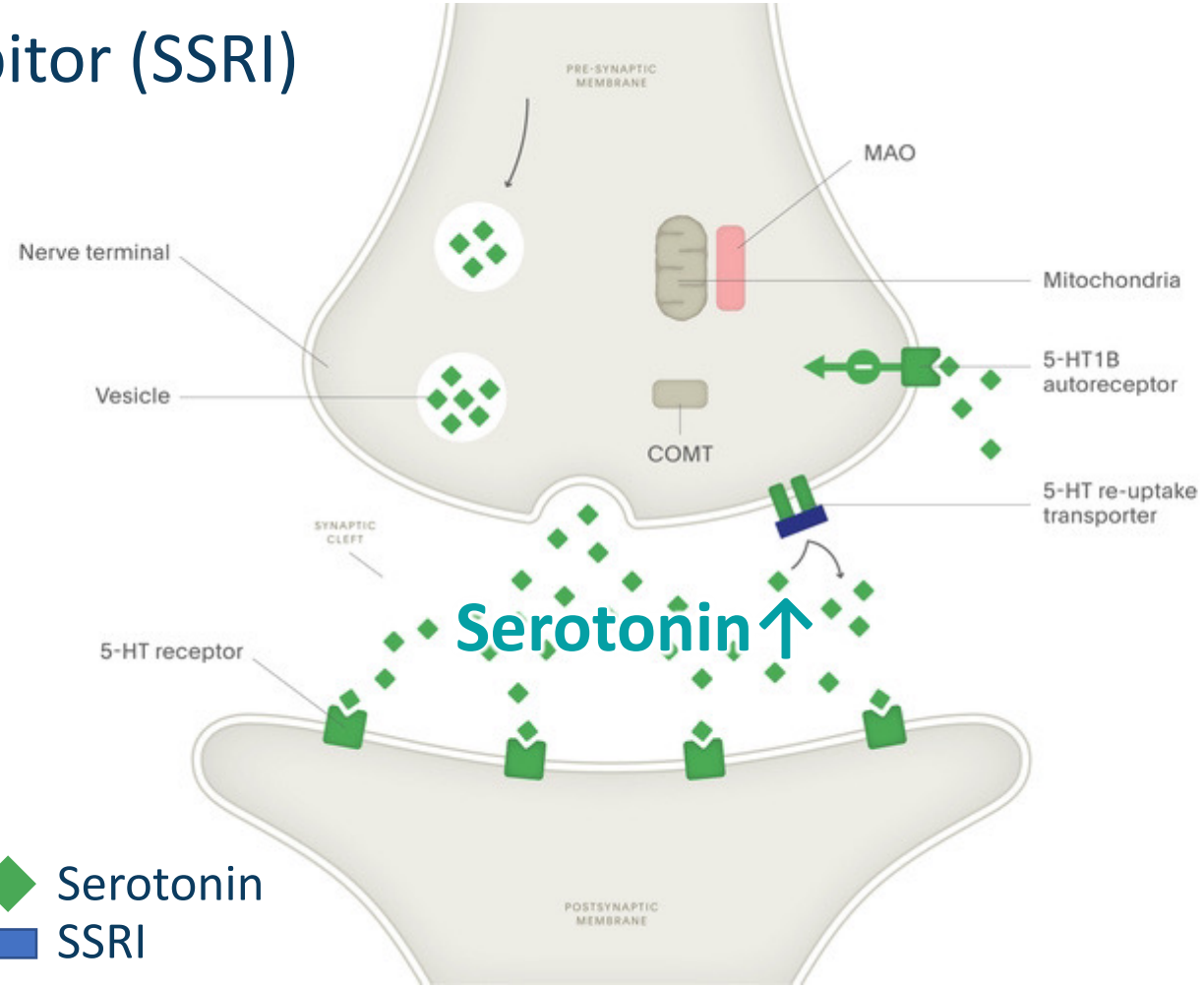
# CNS – Topiramate

- Feline idiopathic ulceration
- **Topiramate** (5 mg/kg, q12h)

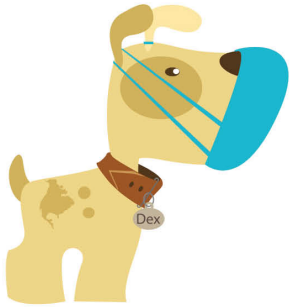
4 weeks later

# Systemic Drug – SSRI

- Selective serotonin reuptake inhibitor (SSRI)
  - Amitriptyline (TCA)
  - Clomipramine (TCA)
  - Doxepin (TCA)
  - Fluoxetine
- Acral lick dermatitis
- cAD?




*TCA: tricyclic antidepressant




# Any Questions?


Chie Tamamoto-Mochizuki

cmochiz@ncsu.edu

NAVDF