THE UNIVERSITY OF BRITISH COLUMBIA
PHARMACEUTICAL SCIENCES

Peripheral Neuroplasticity and Pain

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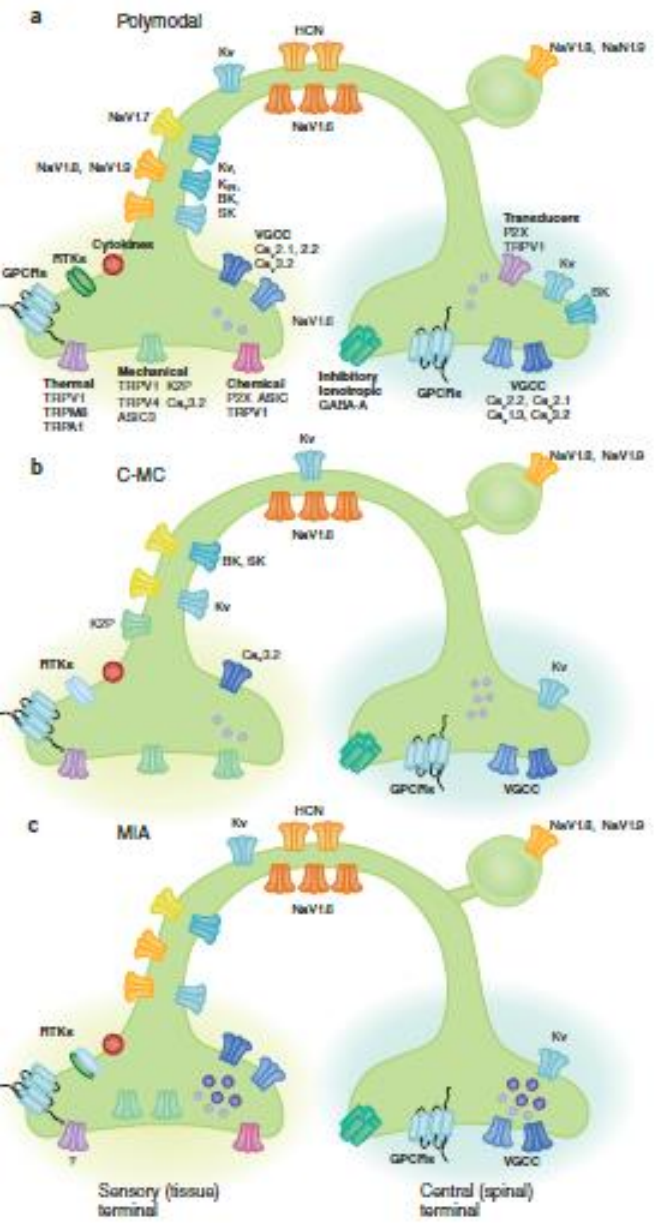
April 28th, 2017

What is peripheral neuroplasticity?

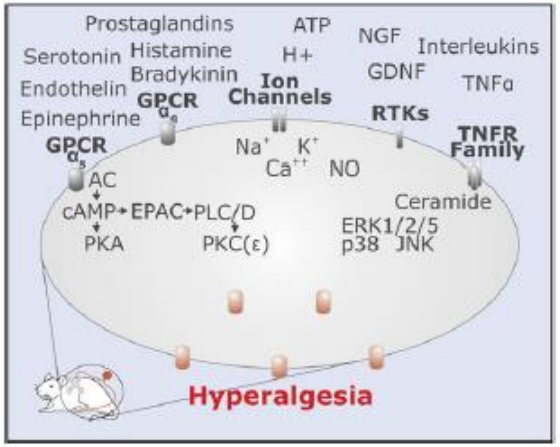
Neuroplasticity refers to the ability of neurons to form new connections to compensate for injury and disease and to adjust their activities in response to new situations or to changes in their environment.

Peripheral neuroplasticity is the compensation by primary afferent fibers to injury or disease and can involve alterations in signalling pathways, protein expression and interactions with autonomic efferent fibers leading to prolonged functional, phenotypic and structural changes.

Nociceptors can undergo neuroplastic changes that categorized as



Gold & Gebhart 2010



sensitization
desensitization
priming

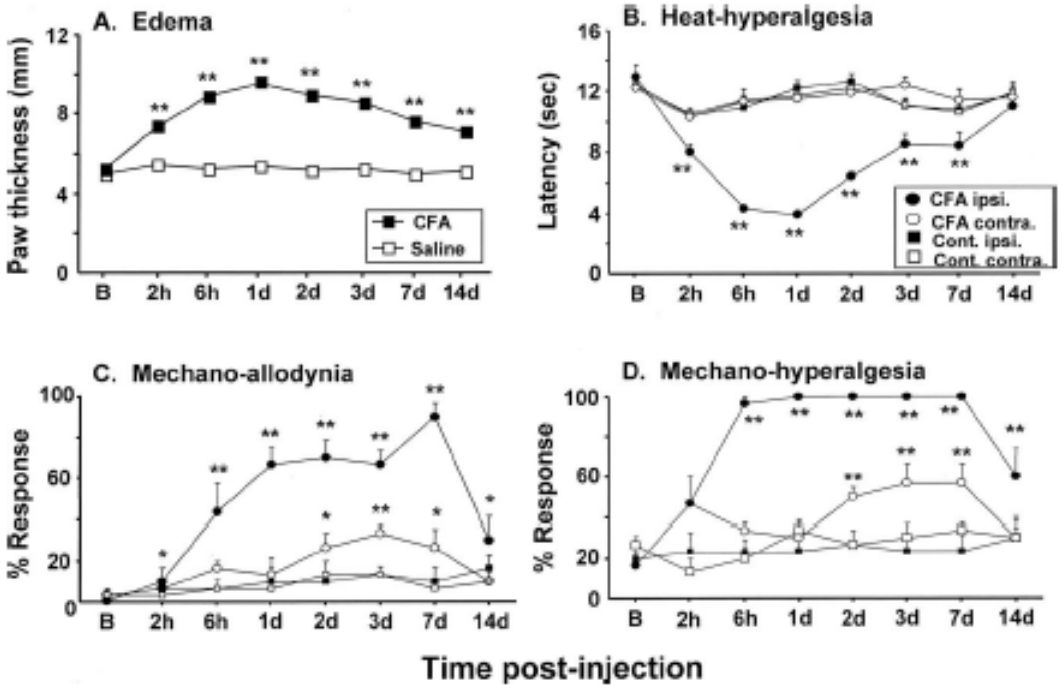
Nociceptor sensitivity is modulated by action of a great many neuroactive substances (e.g. inflammatory soup) that act on a wide variety of GPCRs and ion channels expressed by nociceptors.

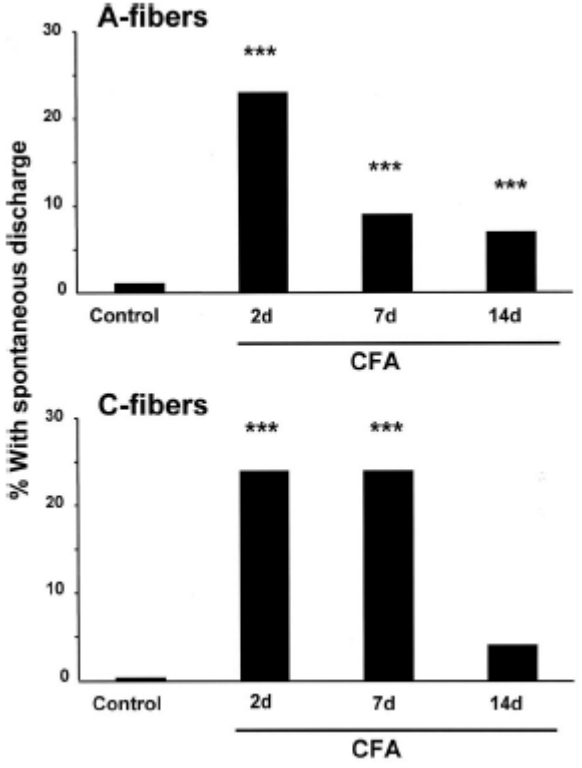
Downstream signalling mechanisms and the targets they alter to modifiy nociceptor responsiveness are a focus of active research.

Peripheral Sensitization and Pain

Complete Freund Adjuvant (CFA) induced inflammation results in a persistant irregular low frequency discharge < 1 Hz in up to 25% of nociceptors

Lowered activation thresholds





Xiao &Bennett 2007

Consequences of peripheral sensitization:

Ongoing (spontaneous) discharge = Spontaneous pain

Decreased activation threshold = Allodynia

Increased action potential firing & after discharges = Hyperalgesia

Mechanisms:

Neurogenic inflammation

Alteration of receptor function

Phenotypic switch

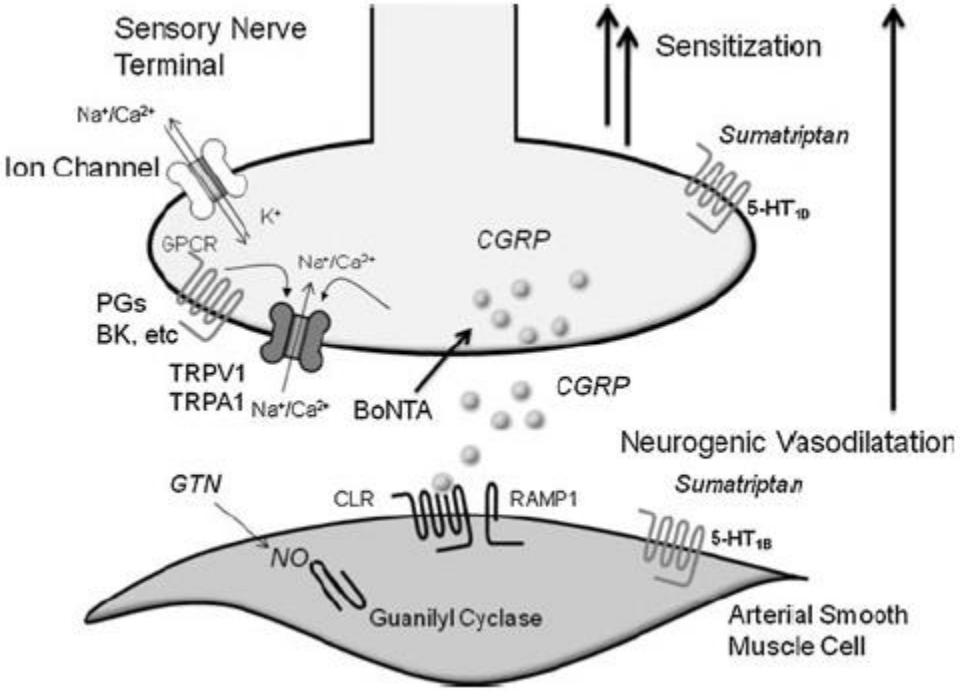
Sensory-autonomic interaction

Priming

Neurogenic Inflammation

release of inflammatory mediators causes vasodilation, plasma leakage and mast cell degranulation within the dura mater

activation and sensitization of dural afferent fibers



J Headache Pain (2012) 13:103–111

calcitonin gene-related peptide (CGRP) mediates meningeal vasodilatation

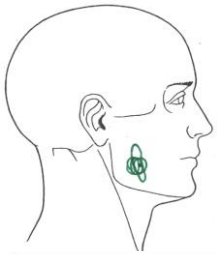
substance P (SP) and neurokinin A (NKA) - plasma extravasation of the dura mater

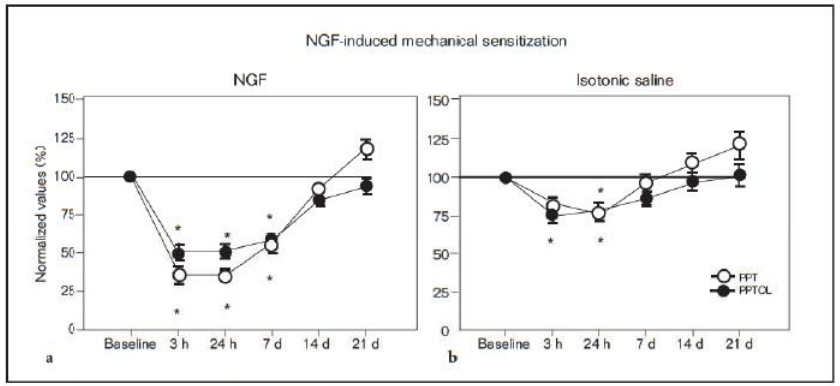
Prostaglandins, bradykinin, glutamate etc sensitize nociceptors

Alteration of Receptor Function

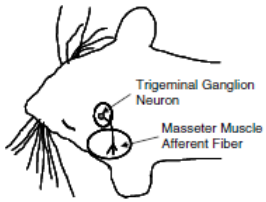
Nerve Growth Factor (NGF) released upon injury to peripheral nerves

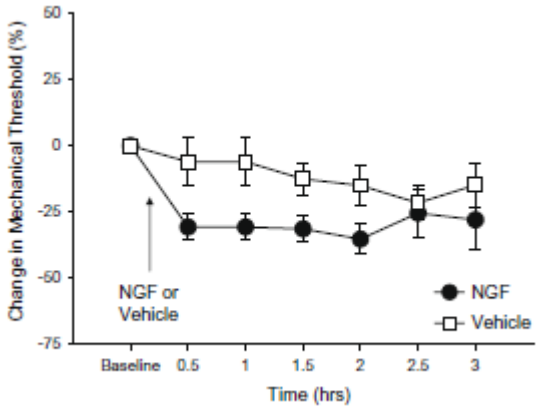
rapidly induces peripheral sensitization in humans and rats

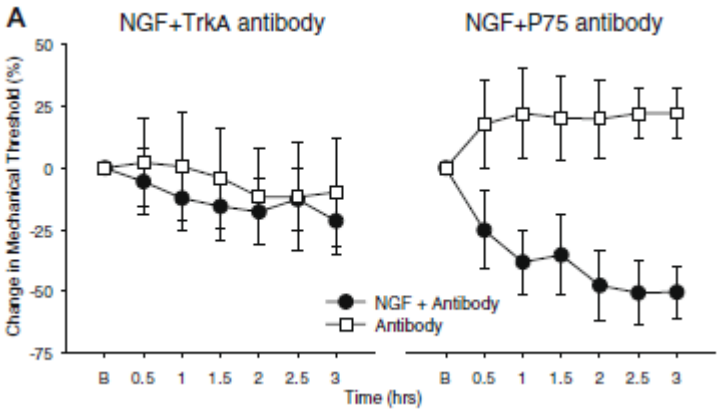




Figs 1a and 1b Normalized PPT and PPTOL values in the masseter muscle at baseline and at various timepoints after administration of *(a)* NGF or *(b)* isotonic saline in women (n = 14; mean values ± SEM). * Indicates values significantly different from baseline values (Tukey: $P < .05$).



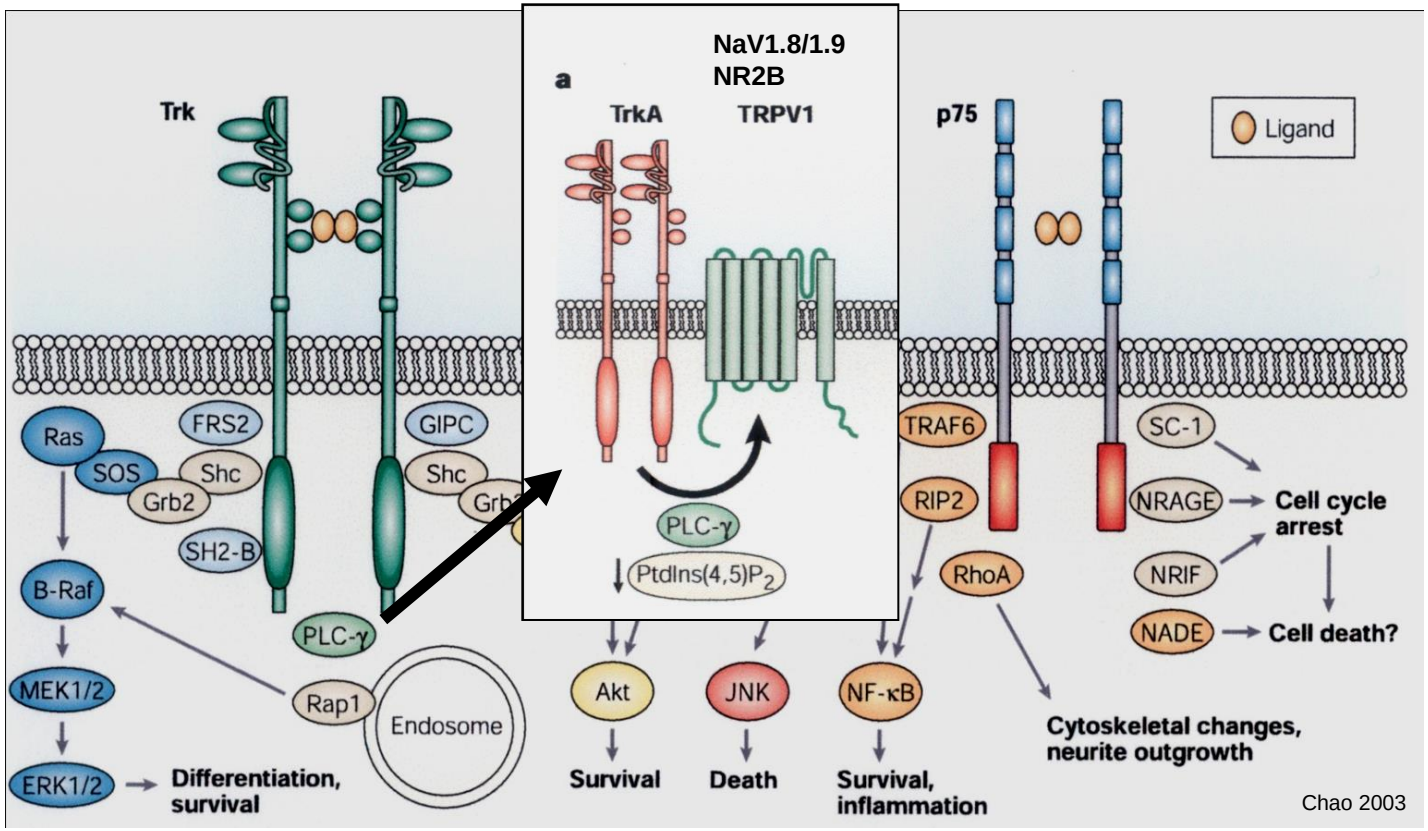




Svensson et al 2008, 2010

Alteration of Receptor Function

Phosphorylation of TrpV1 and NMDA channels results in slowed desensitization and increased current which increases nociceptor responsiveness to heat and mechanical stimulation.



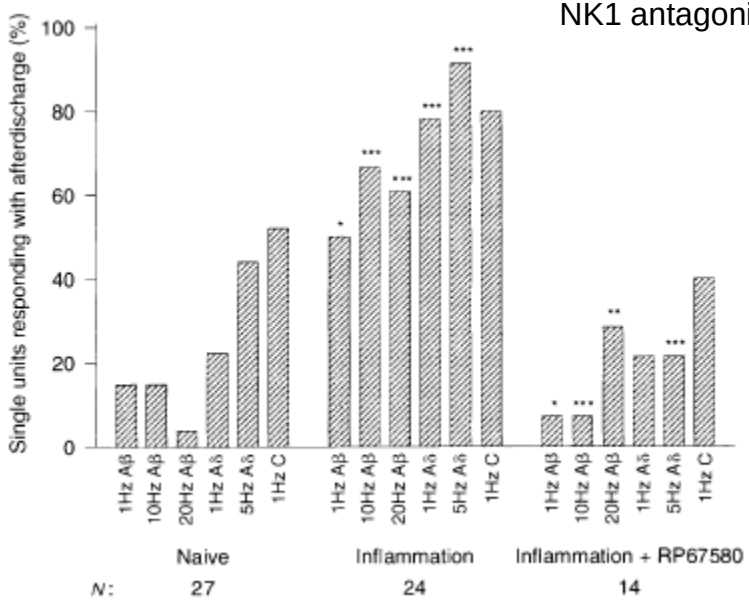
Phenotypic switch

low threshold afferents acquire pain-provoking properties

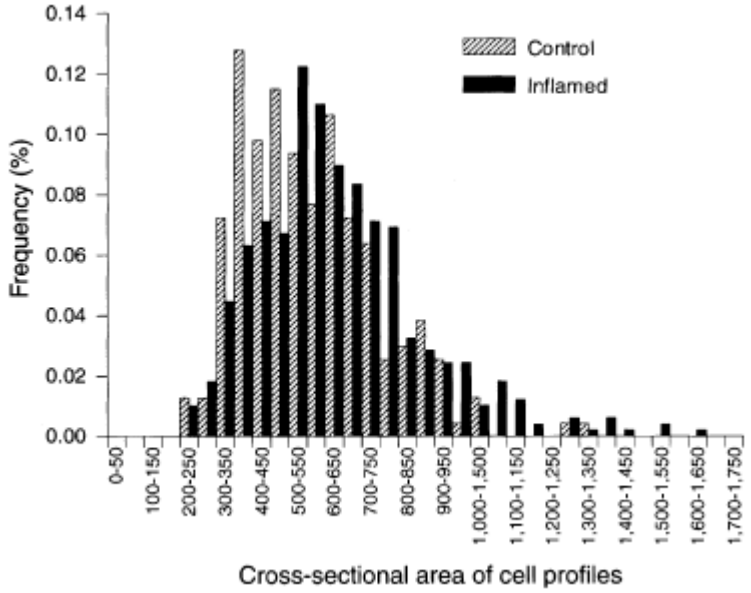
after inflammation or nerve injury, Aβ fibers start firing spontaneously and selective activation of these fibers causes after-discharges in nociceptive spinal cord neurons.

injury also increases the number of ganglion neurons that begin to express neuropeptides (substance P, BDNF, NPY and CGRP)

NK1 antagonist



Substance P expression in DRG



Neuman et al 1996

Phenotypic switch (muscle afferents)

Intramuscular injection of NGF increases the expression of peripheral NMDA receptors in larger diameter neurons.

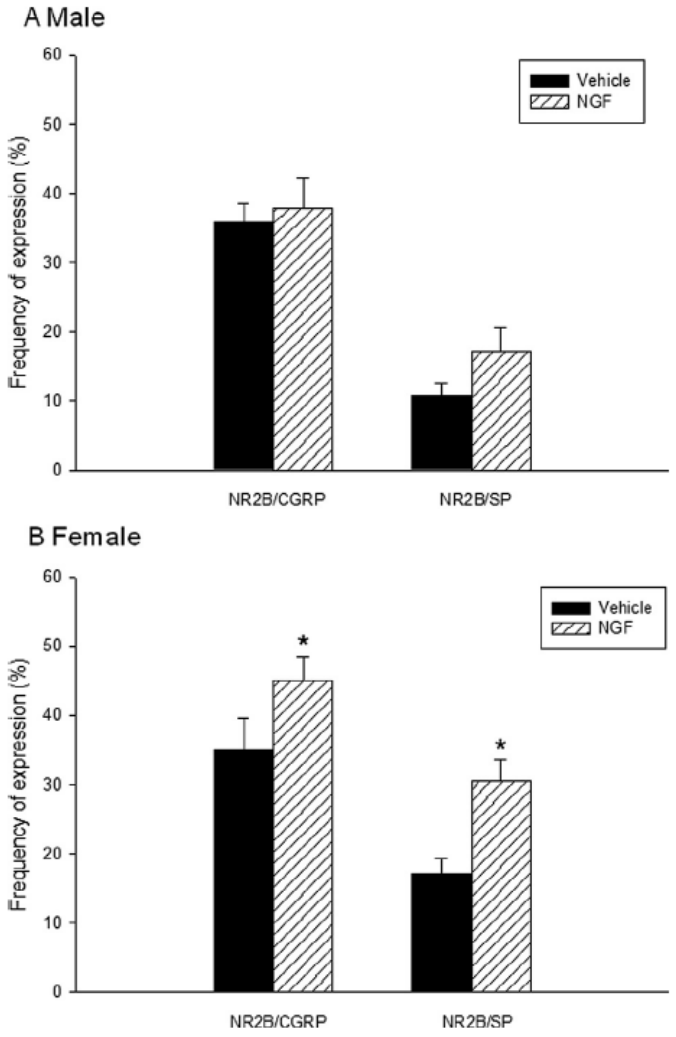
the number of afferent fibers expressing substance P and CGRP is increased.

This change is greater in females than in males.

Table 1. The median cross sectional somata size of NR2B subunit-immunopositive trigeminal masseter ganglion neurons following intramuscular NGF injection

Group	Male		Female	
	N	Median (μm^2)	*N*	Median (μm^2)
Naive	122	766	121	744
1 day	180	1111*	132	930*
3 days	203	1060*	363	1020*
7 days	229	983*	293	949*
14 days	174	722	115	950*

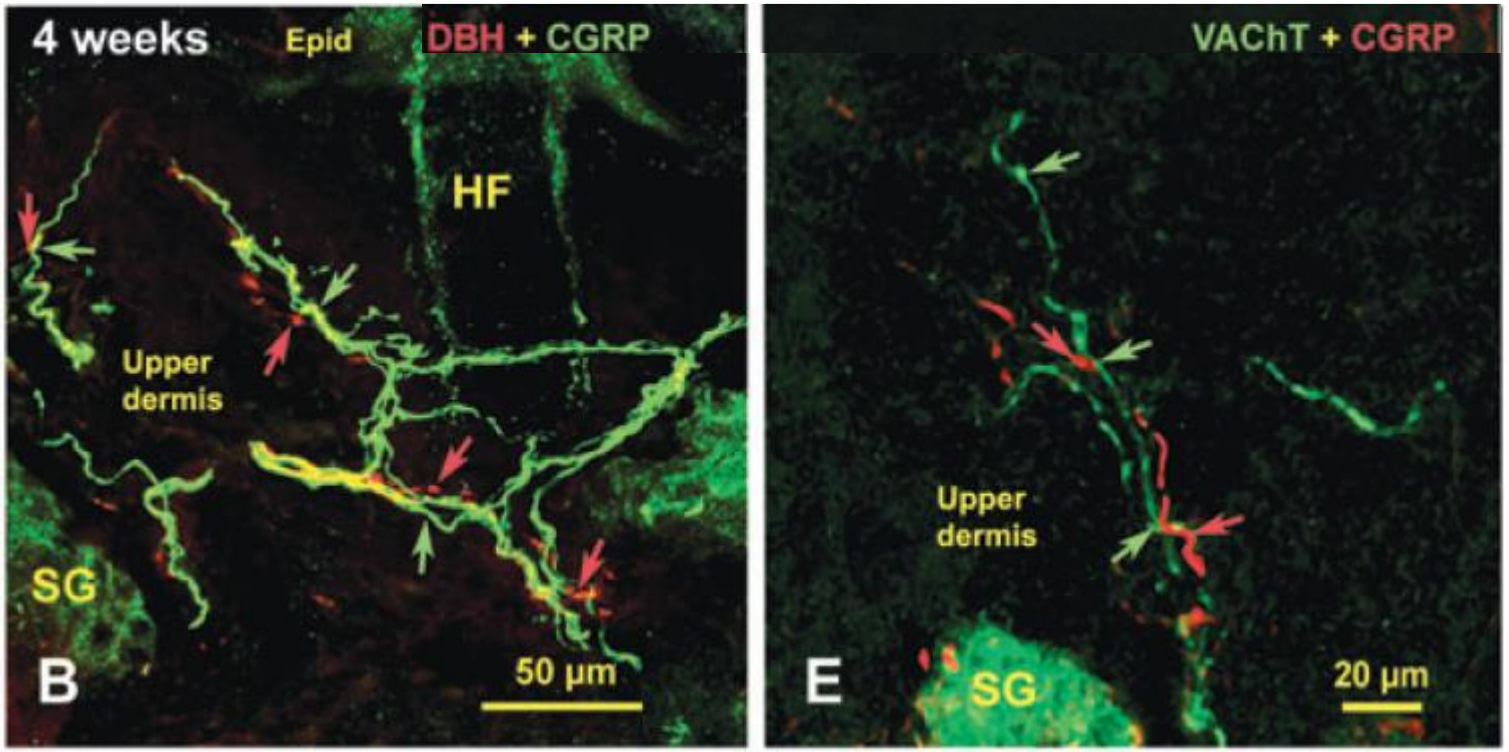
Data from each treatment group was pooled for analysis. Asterisks denote significant difference from pre-NGF injection baseline value by Kruskal–Wallis one way ANOVA on ranks ($p < 0.05$).



Wong et al 2014

Autonomic Sensory Interactions

4 weeks after mental nerve ligation, extensive sprouting of sympathetic (DBH) and parasympathetic (VAChT) into skin territory innervated by the damaged nerve.



Autonomic fibers come into close contact with sensory fibers (CGRP positive), suggesting the possibility of an interaction.

Grelik et al 2005

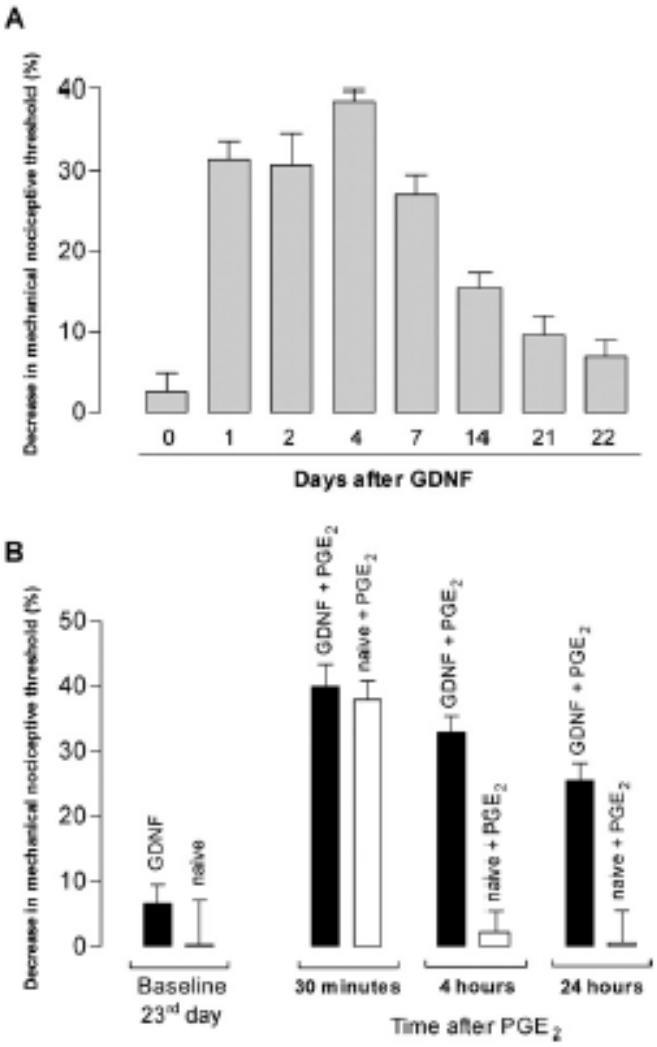
Hyperalgesic Priming

Lowered threshold for sensitization produced by an initial priming stimulus (that is no longer altering function).

Carrageenan, NGF or GDNF induce cutaneous mechanical sensitization.

after the end of the mechanical sensitization, an injection of PGE2 produces up to 24 hours of mechanical hyperalgesia than in animals give only control injection.

GDNF-Induced Hyperalgesic Priming



Ferrari et al 2010.

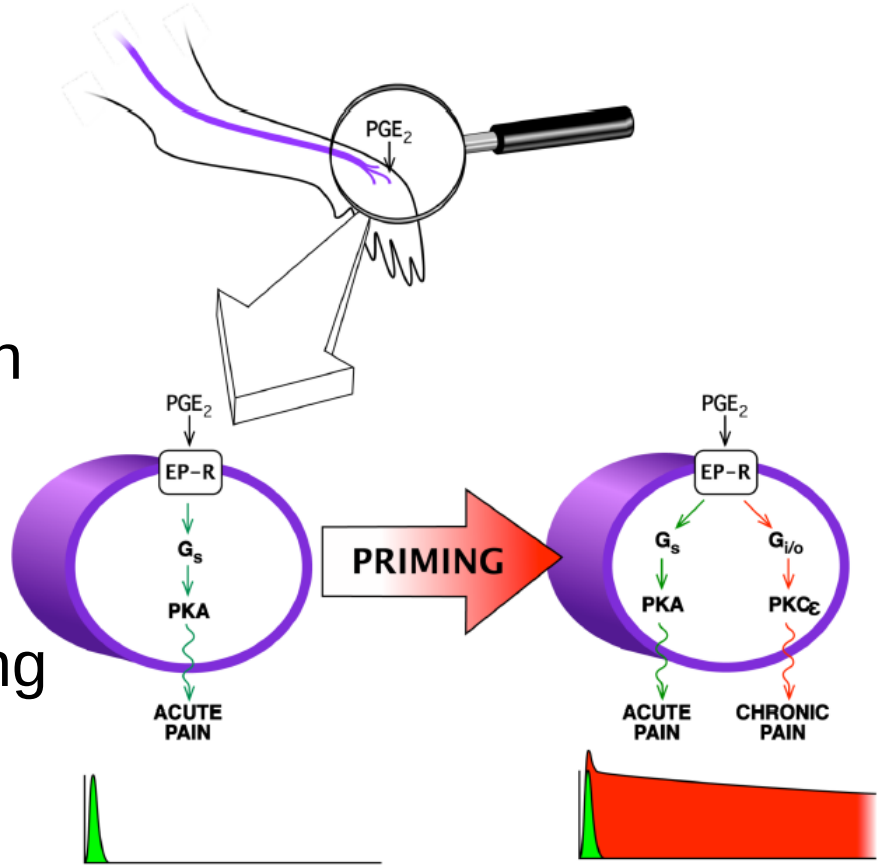
Hyperalgesic Priming

also shifts the dose response relationship for PGE2-induced hyperalgesia to the left – and 5-HT adenosine

PGE2 normally activates the protein kinase A (PKA) pathway in afferent terminals.

Priming alters this receptor signalling cascade (e.g. from inhibitory to excitatory) to also recruit protein kinase C epsilon (PKCe)

Is this a model of re-injury pain or stress-induced pain?



Rechling and Levine 2009

Ectopic Action Potential Generation and Peripheral Neuroplasticity

There are normally no synapses in sensory ganglia (except for the mesecephalic nucleus), but ganglion neurons and terminal endings have many of the same receptors as central neurons.

Initiation of action potentials from a part of the primary afferent fiber other than the terminal ending of the afferent fiber, e.g. from a neuroma

Action potentials can be initiated along axons and by depolarization of sensory ganglion neurons. This can be a consequence of altered receptor expression or interactions between the ganglion neuron and its supporting glial cells or immune cells.

The brain interprets these signals as originating in the tissue that the afferent fiber innervates, despite the fact that they are not generated by a change in the tissue.

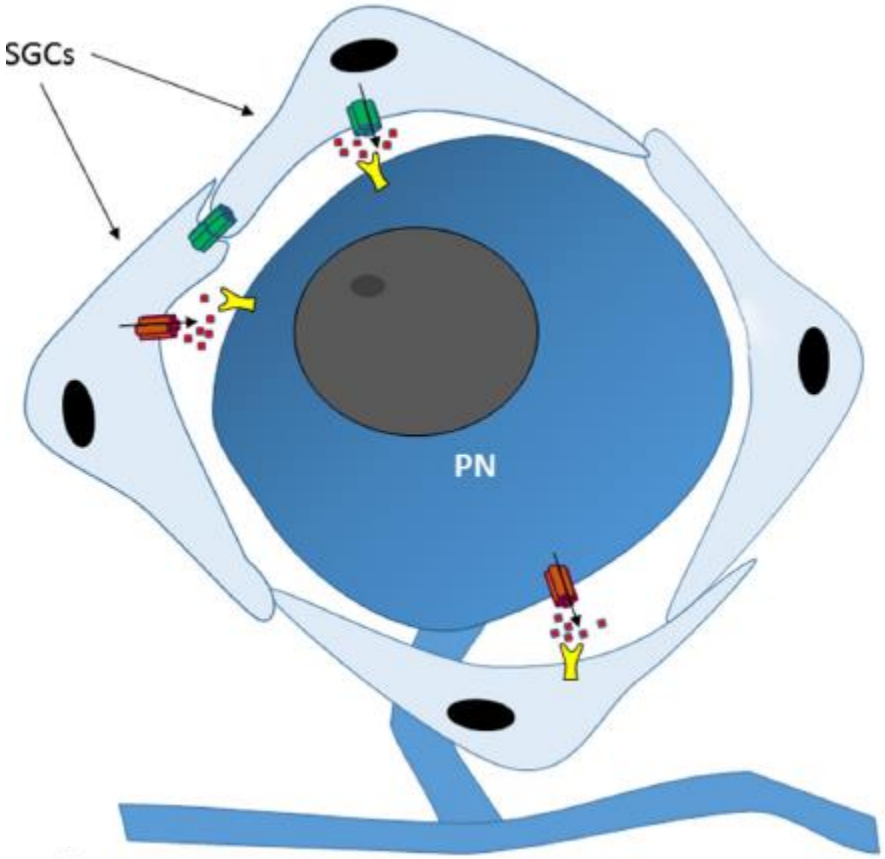
Sensory Ganglia:

Satellite Glial Cells surround monopolar neurons of sensory fibers in ganglia and are similar to astrocytes

connected by gap junctions, which allow communication between adjacent cells

soma of sensory afferent fibers can release neurotransmitters that affect the function of SGCs

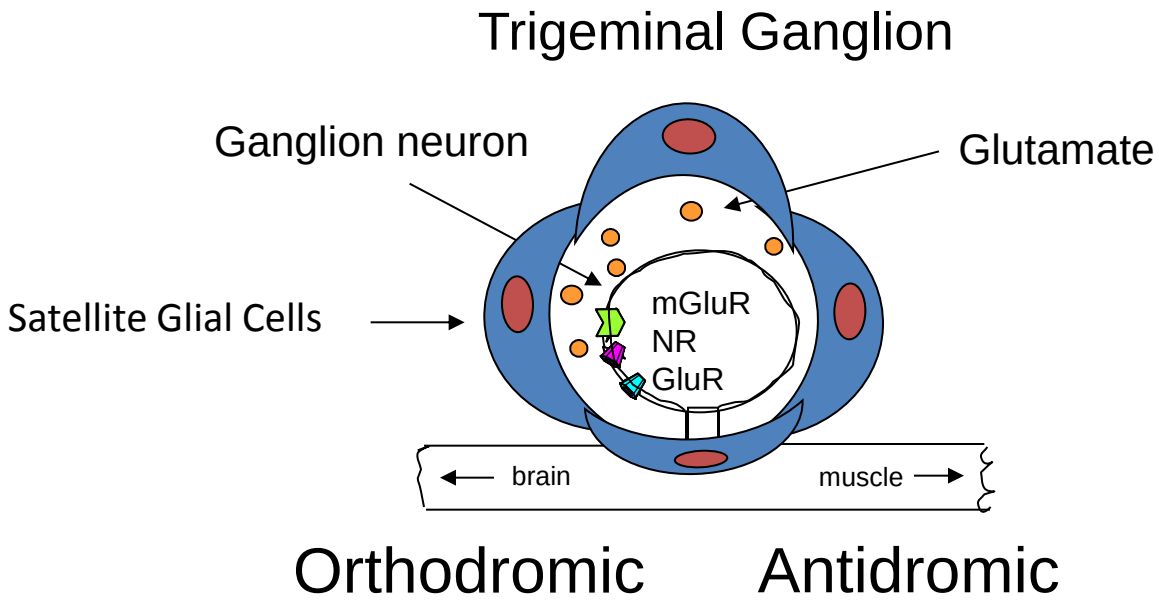
SGCs may release substances which affect the activity of the soma as well



Trigeminal Ganglion

In vitro, trigeminal ganglion neurons release glutamate.

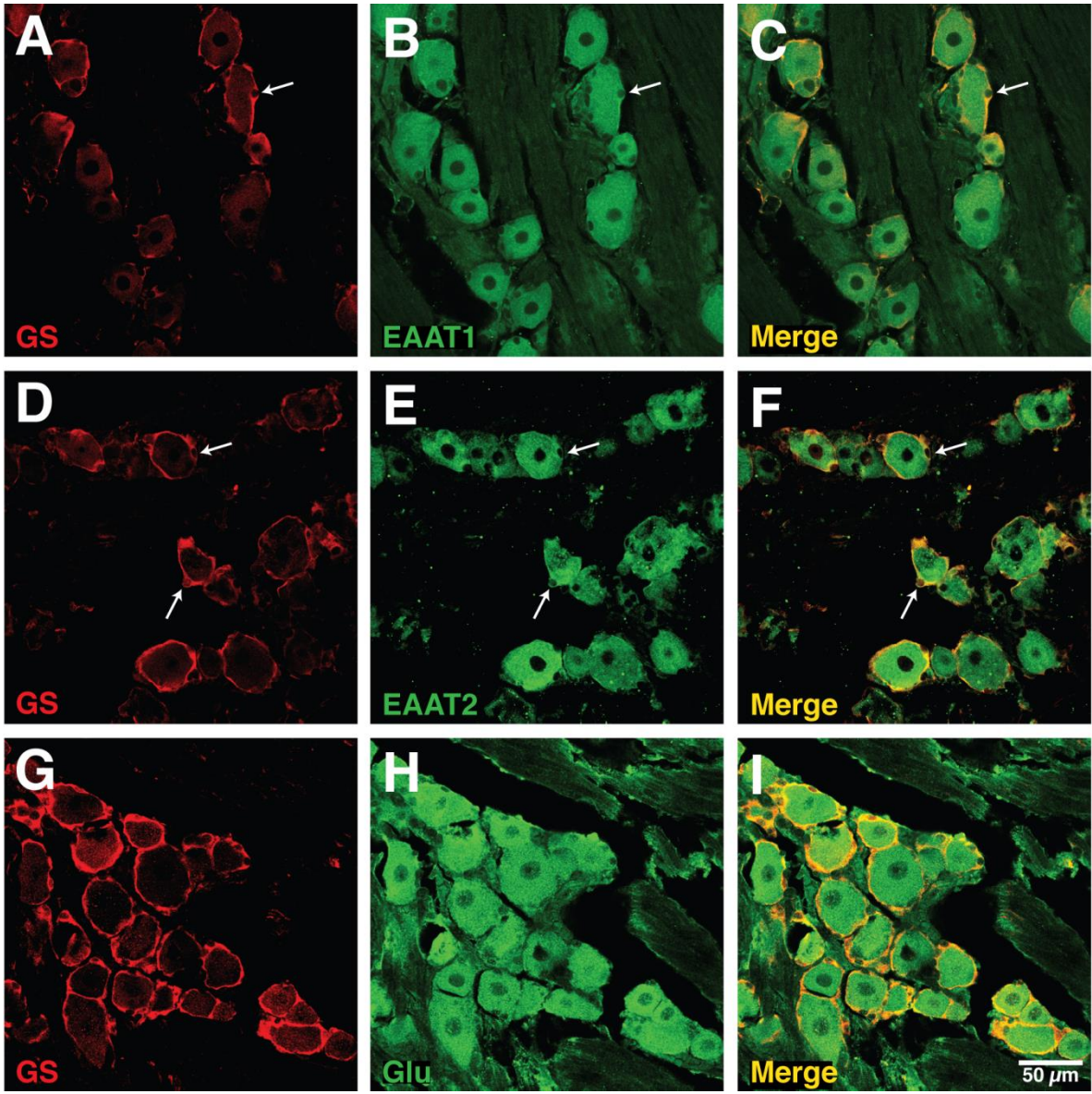
Do SGCs store glutamate (like astrocytes)? Can activated SGCs release glutamate? What would the consequence of elevated glutamate be on the activity of ganglion neurons?



Trigeminal Satellite Glial Cells

In the trigeminal ganglion satellite glial cells, which express glutamine synthetase, surround trigeminal ganglion neurons.

Satellite glial cells and trigeminal ganglion neurons express excitatory amino acid transporters (EAATs) and contain glutamate.



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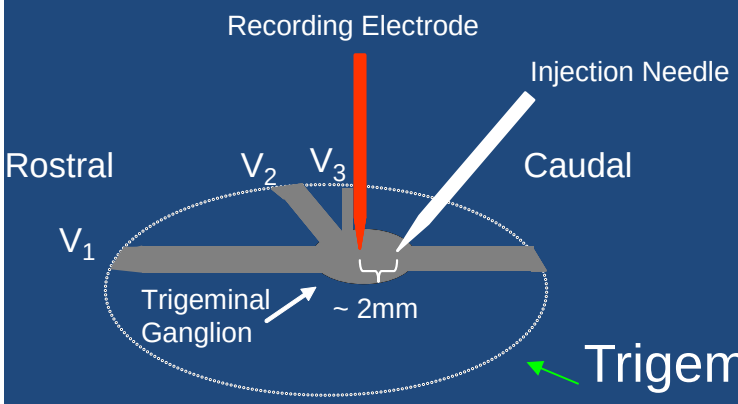
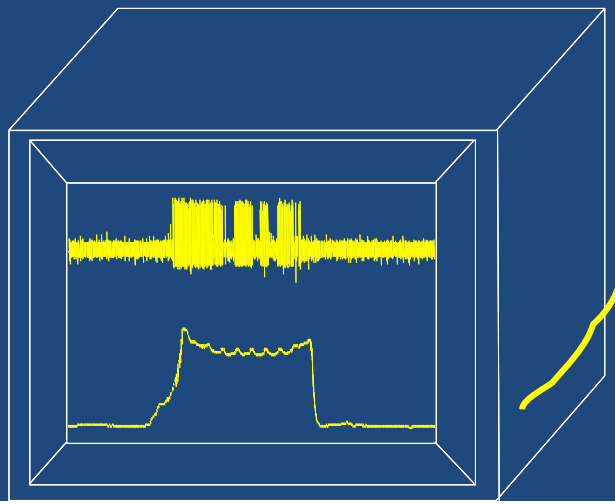
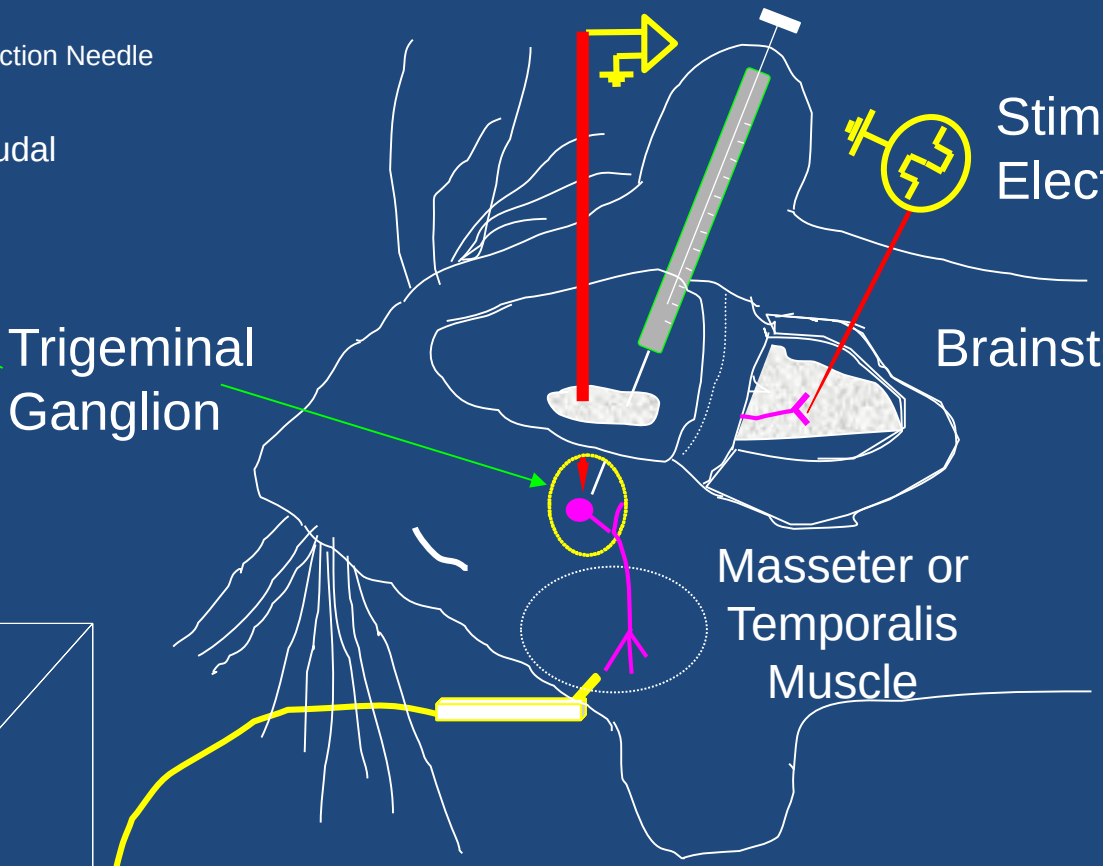
Experimental Set-up

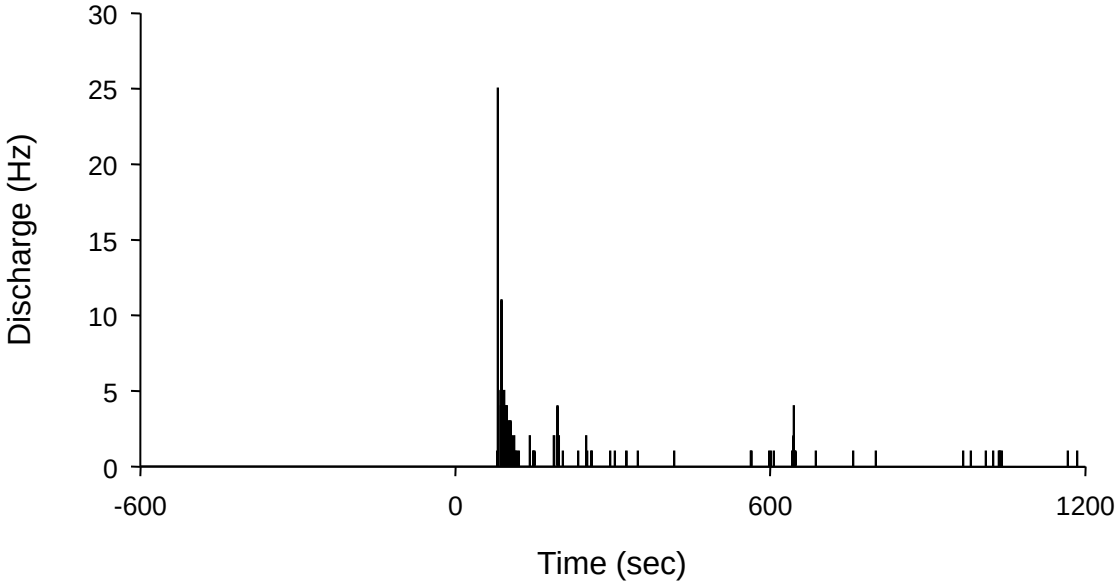




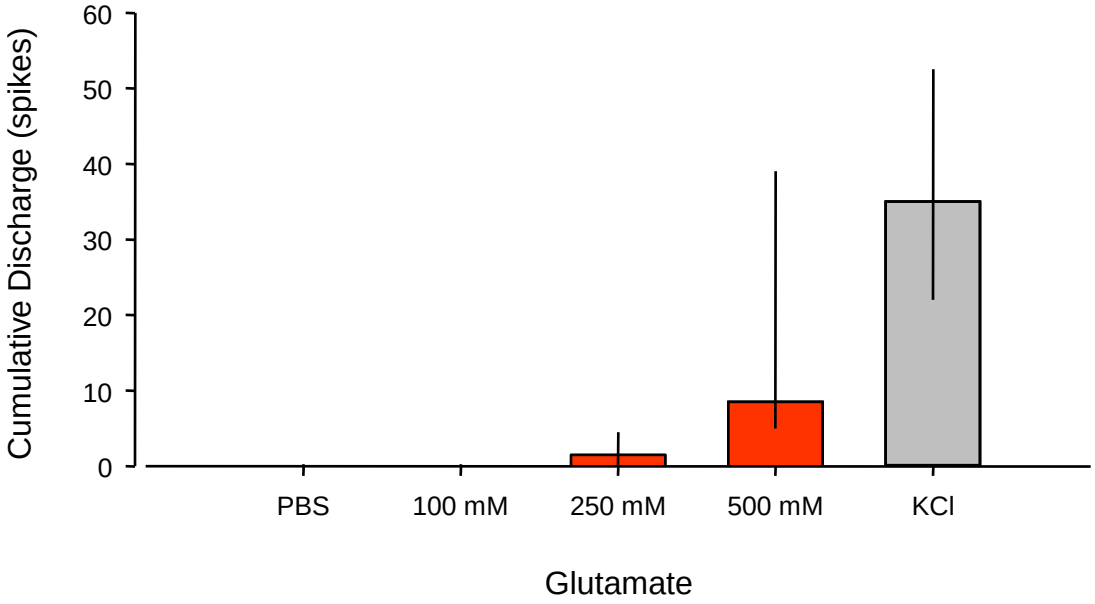


Increases in intraganglionic glutamate concentration excite trigeminal ganglion neurons

Intraganglionic injection of glutamate (3 μl) into the trigeminal ganglion evokes discharge



Discharge increases with increasing glutamate concentration



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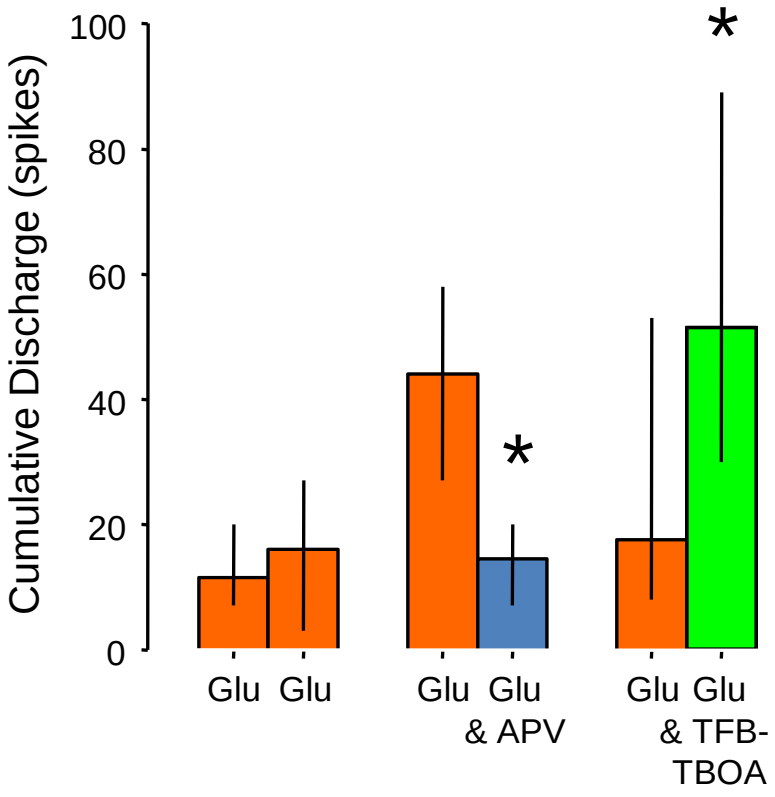
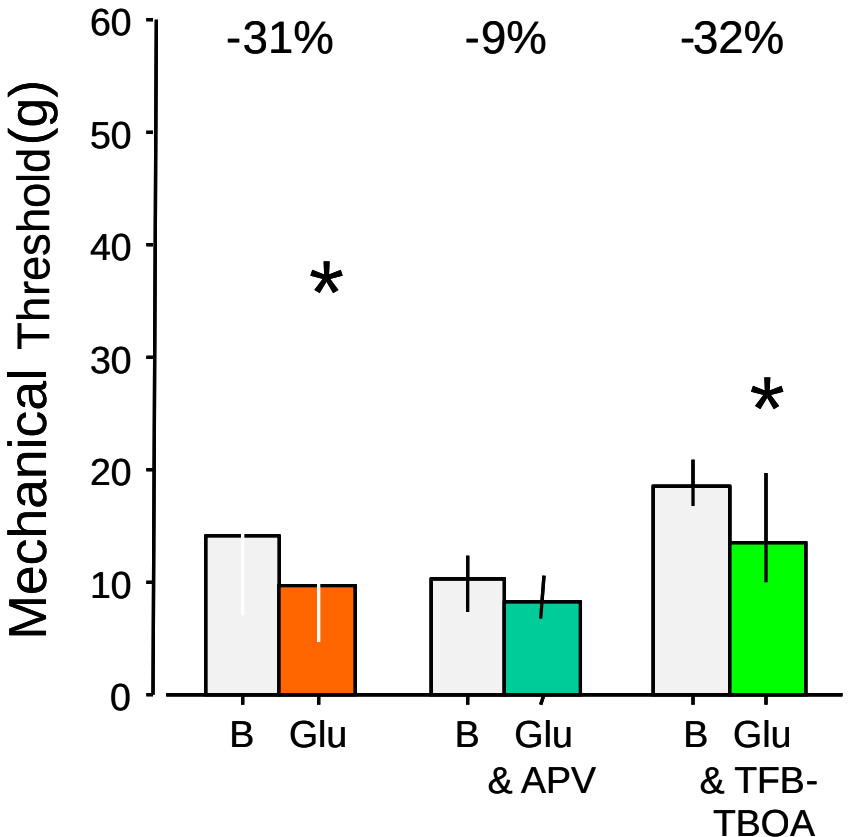
Reproducible discharges can be evoked by intraganglionic injection of glutamate and increased by EAAT inhibition.

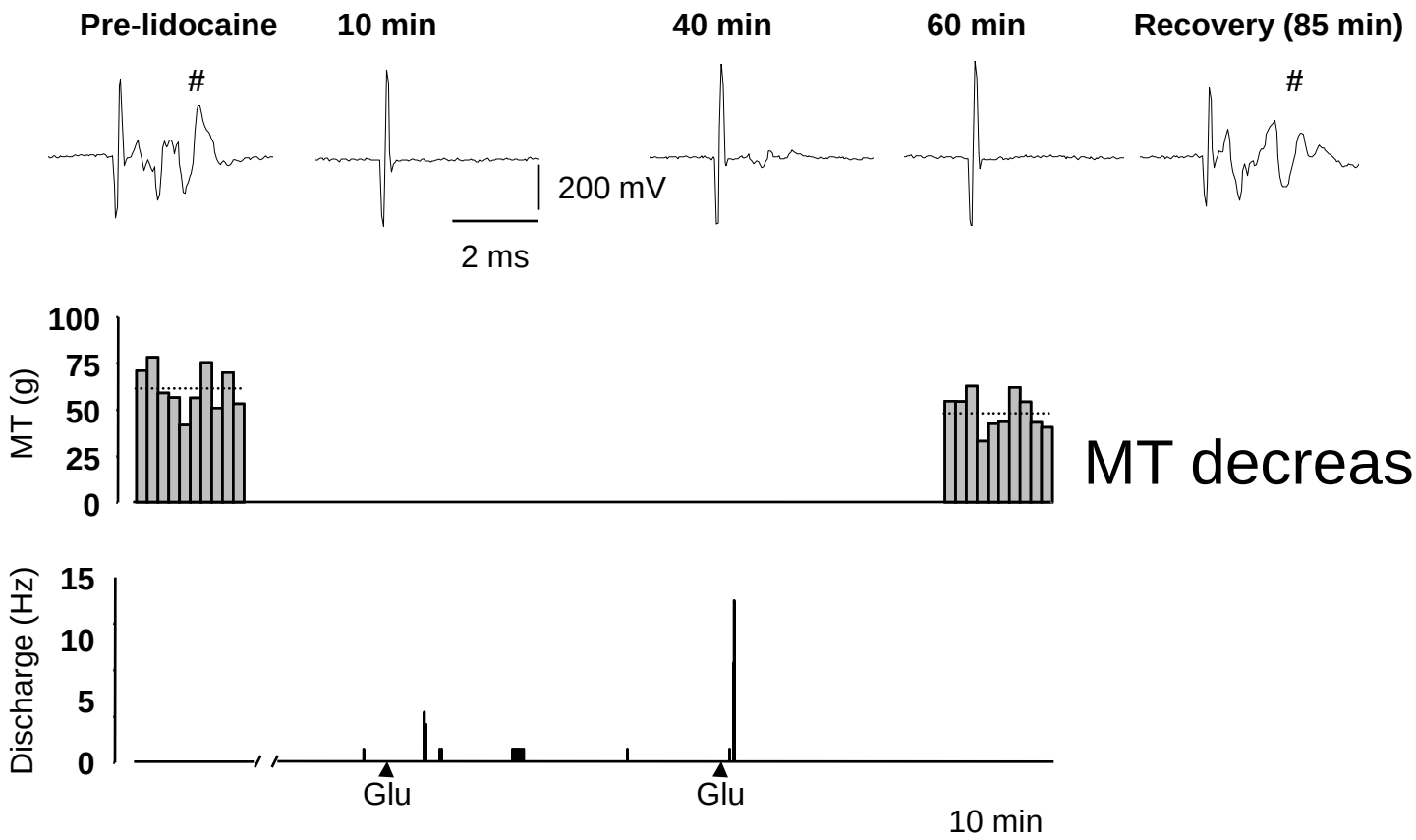
Mechanical sensitization induced by intra-ganglionic injection of glutamate

Discharge and sensitization attenuated by the NMDA receptor antagonist APV





Application of lidocaine to the brainstem blocked afferent input but had no effect on the ability of intraganglionic injections of glutamate to induce mechanical sensitization.



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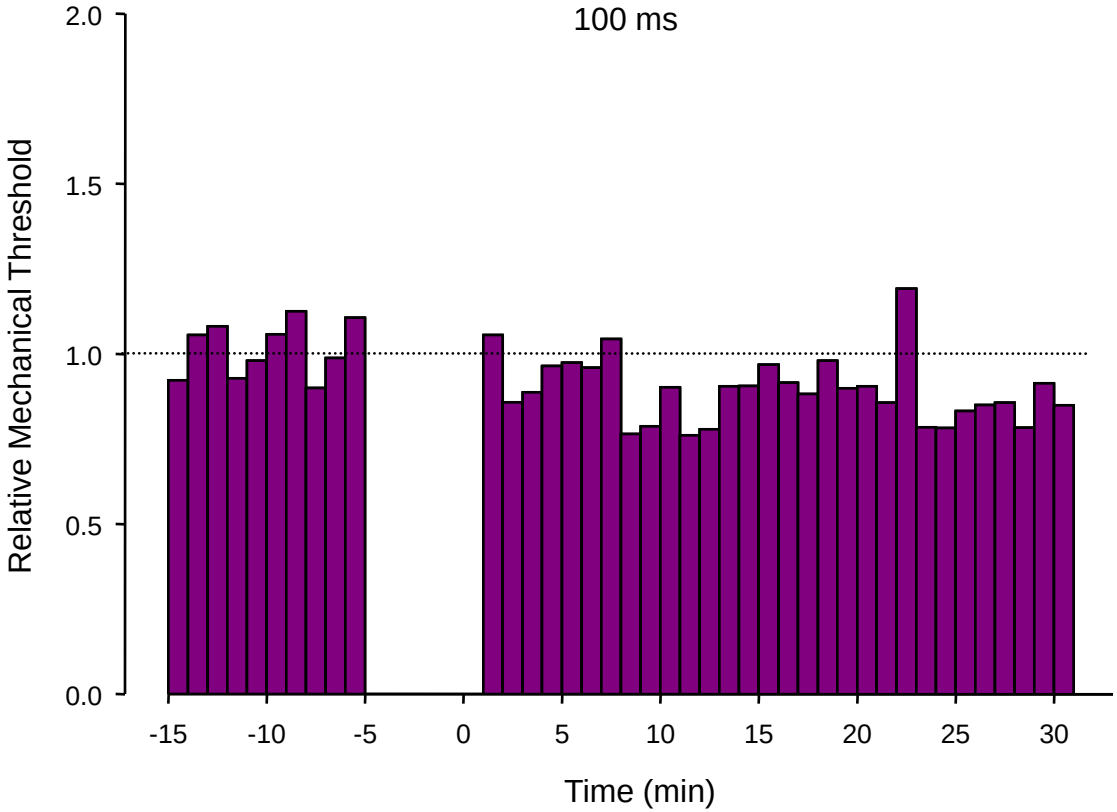
Mechanical sensitization is not due to entirely to neurogenic inflammation.

C-fibre

10 Hz antidromic stimulation

10 Hz antidromic stimulation does not significantly alter mechanical threshold



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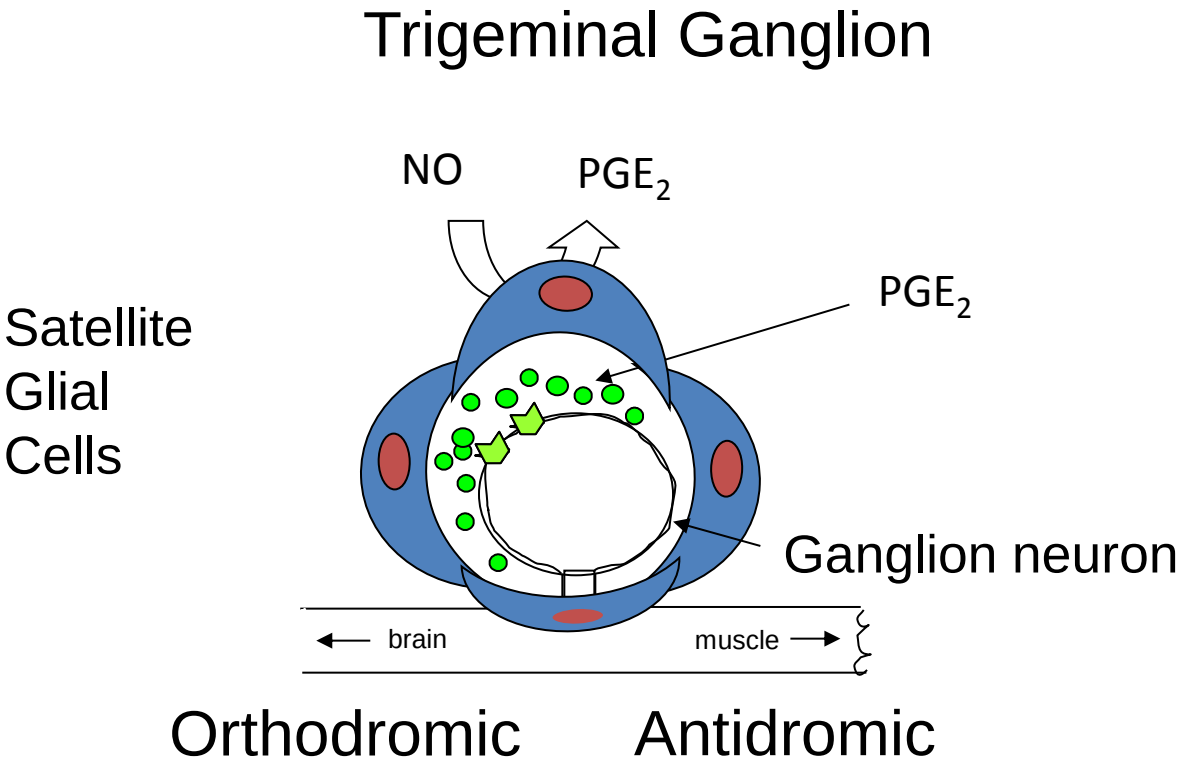
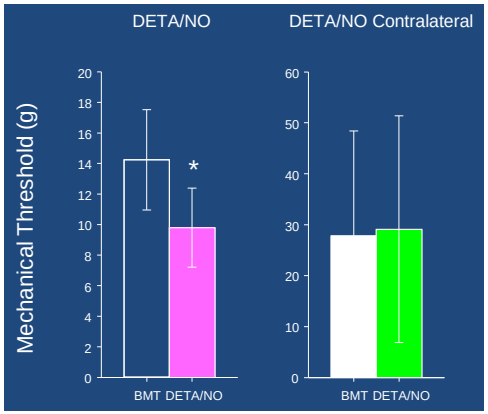
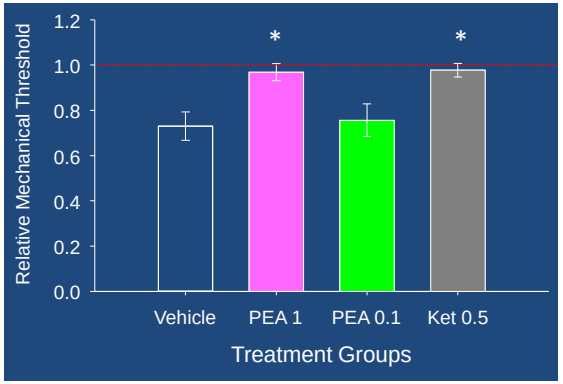
Intra-ganglionic Injection of Nitric Oxide (NO)







NO does not evoke action potential discharge but does induce peripheral mechanical sensitization

NO causes SGCs to release PGE2. NO-induced sensitization is blocked by NSAIDs and palmitoylethanolamide

Cairns et al 2014

Summary

-SGCs contain glutamate and express EAATs, and play a role in maintaining glutamate homeostasis in the ganglion.

-Artificial elevation of glutamate concentration in the ganglion causes ectopic discharge that induces peripheral mechanical sensitization.

-NO also induces peripheral mechanical sensitization, but by inducing SGCs to release PGE2 onto ganglion neurons.

-A peripheral mechanism underlies mechanical sensitization, as blockade of ascending sensory transmission does not affect the induction of mechanical sensitization.

-Peripheral neuroplasticity can occur both at the terminal endings and within sensory ganglia to induce long term changes in nociceptive processing.

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