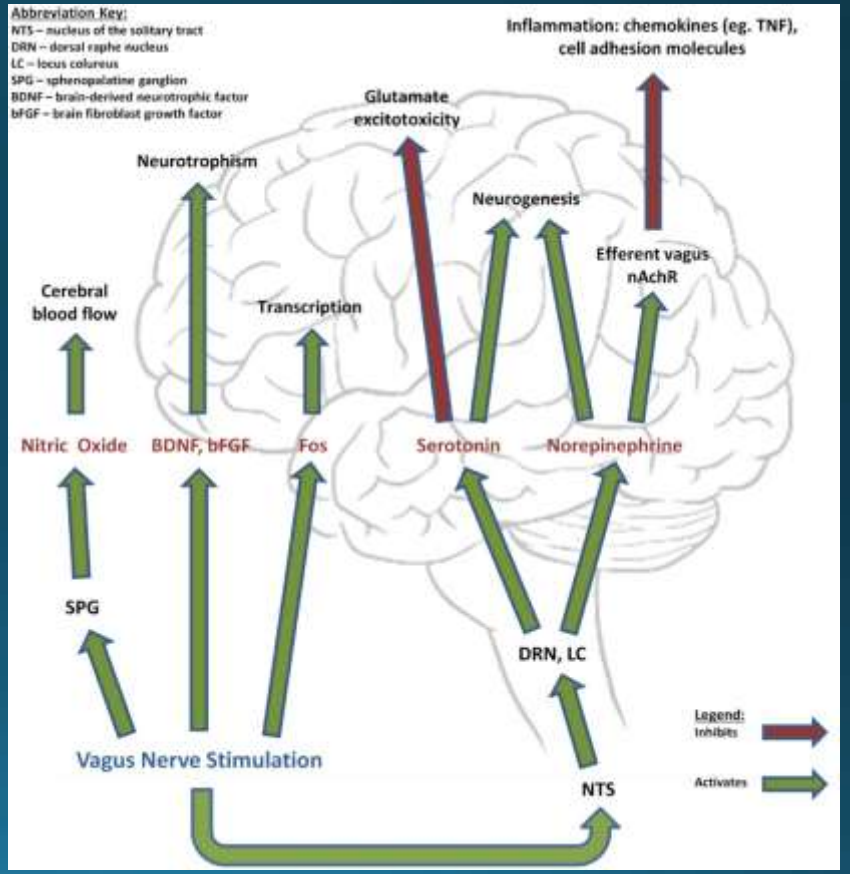
Emerging Novel Treatments for Orofacial Pain

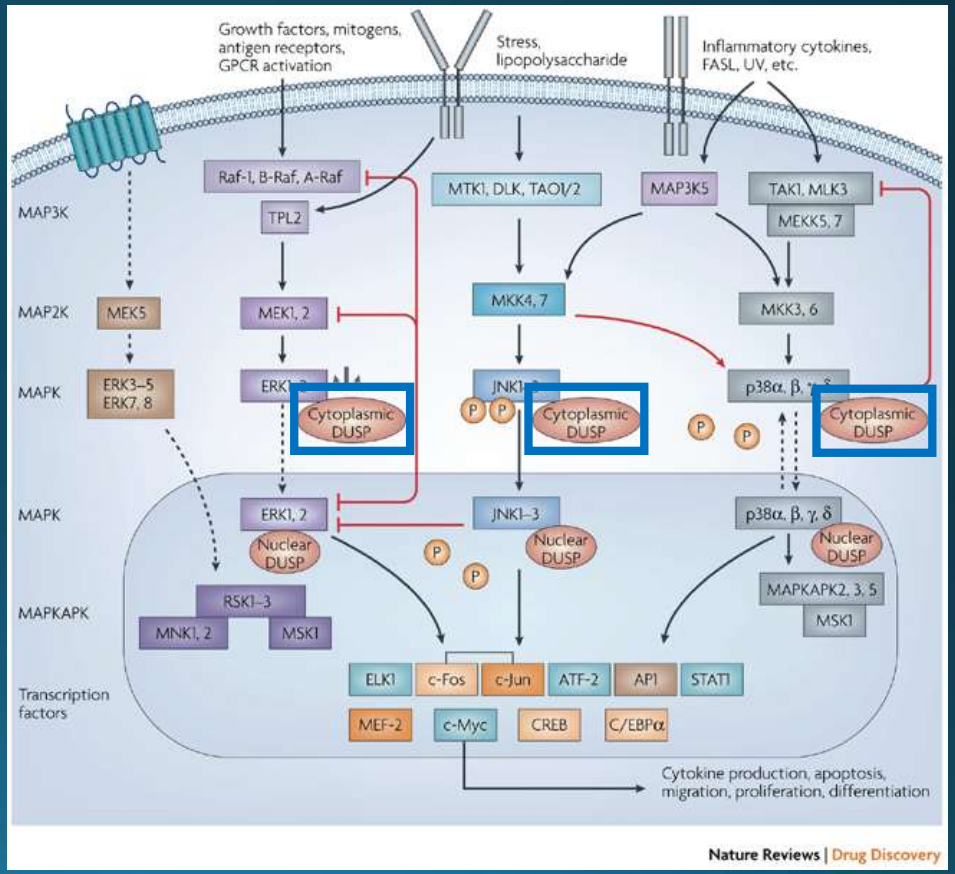


Cannabidiol (CBD)

Increases Phosphatases
Inhibits Nociception
Represses Inflammatory Proteins

Goal of Study

To investigate the effects of a cannabidiol (CBD) extract of industrial hemp derived from a cultivar expressing low levels of Tetrahydrocannabinol (THC) on the levels of MAP kinase phosphatases in trigeminal ganglion, upper spinal cord, and brain as well as changes in cognitive ability.



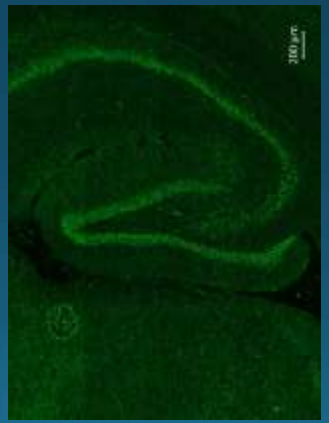
MAP Kinase Phosphatases:

MKP-1 MKP-2 MKP-3

Methods

Adult male or female Sprague-Dawley rats were injected with 2 different doses of a CBD (1 mg/kg and 0.1 mg/kg). After 2, 24, and 48 hours, animals were sacrificed and the trigeminal ganglia, upper spinal cord (C1-3), and the whole brain were removed for further analysis. The experimental design included a minimum of five animals for each condition - naïve unstimulated, vehicle control, and two concentrations of CBD. Immunohistochemistry and image analysis was used to determine the levels of the MAP kinase phosphatases MKP-1, MKP-2, and MKP-3 in ganglia, spinal cord, and brain tissues. In addition, two different cognitive tests were performed including novel object recognition and spatial reference memory, which is known as the Morris Water Maze test.

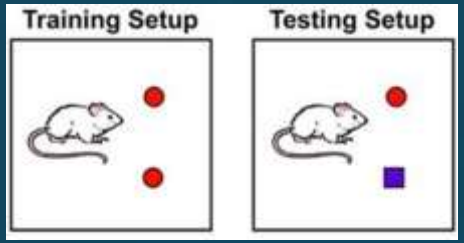
DAPI

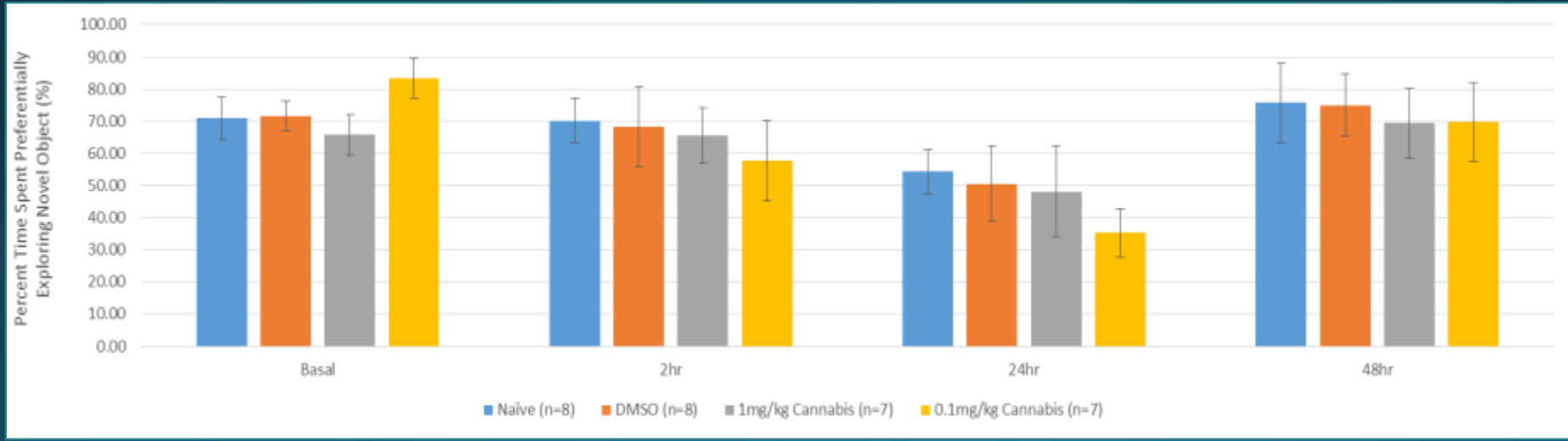


MKP-3

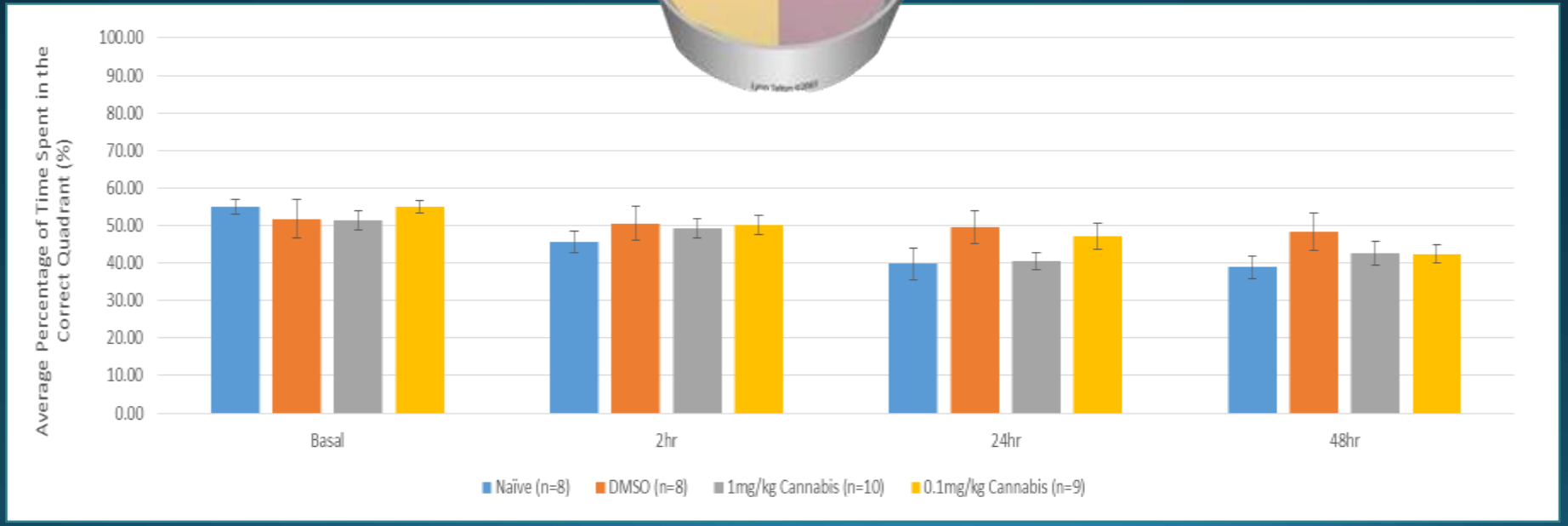
NeuN

CBD Extract Does Not Affect Novel Object Recognition

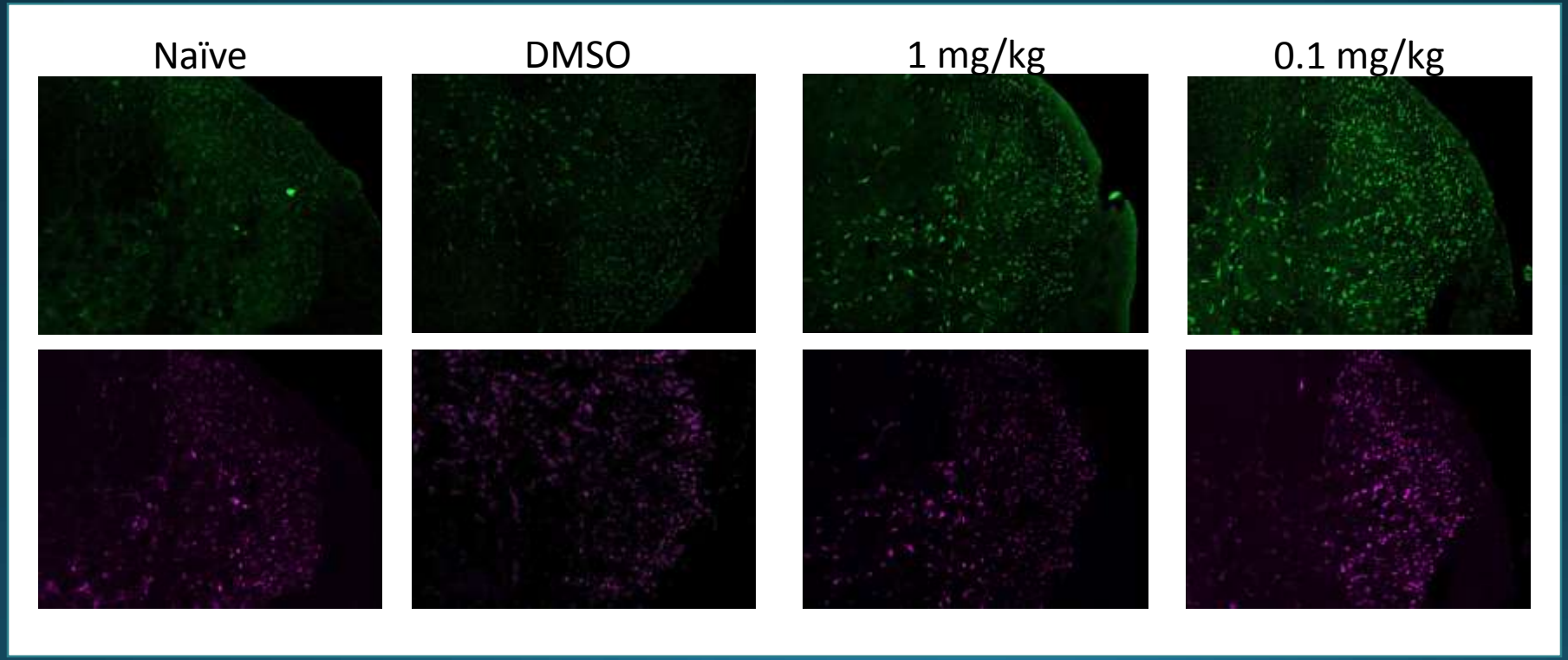




CBD Extract Does Not Affect Spatial Reasoning When Compared to Baseline

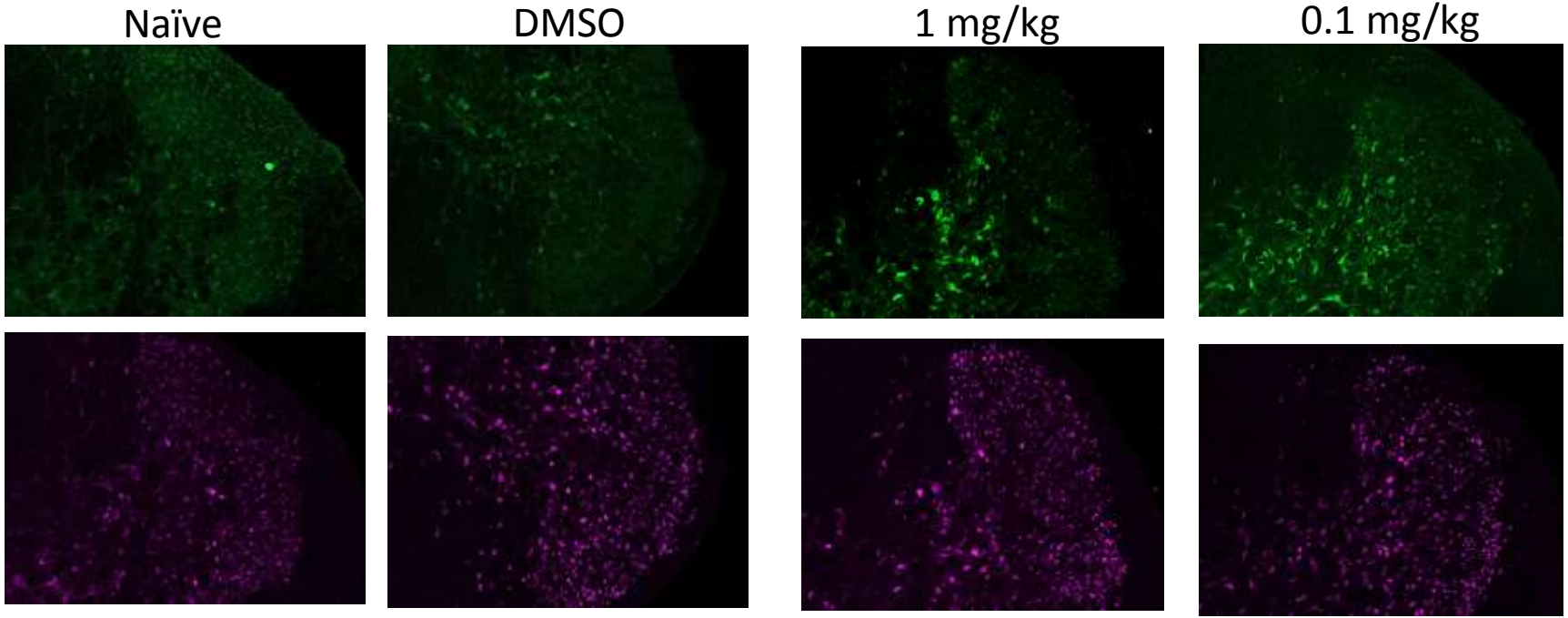


CBD Stimulates Expression of MKP-2 in Dorsal Medullary Horn – 2 hr



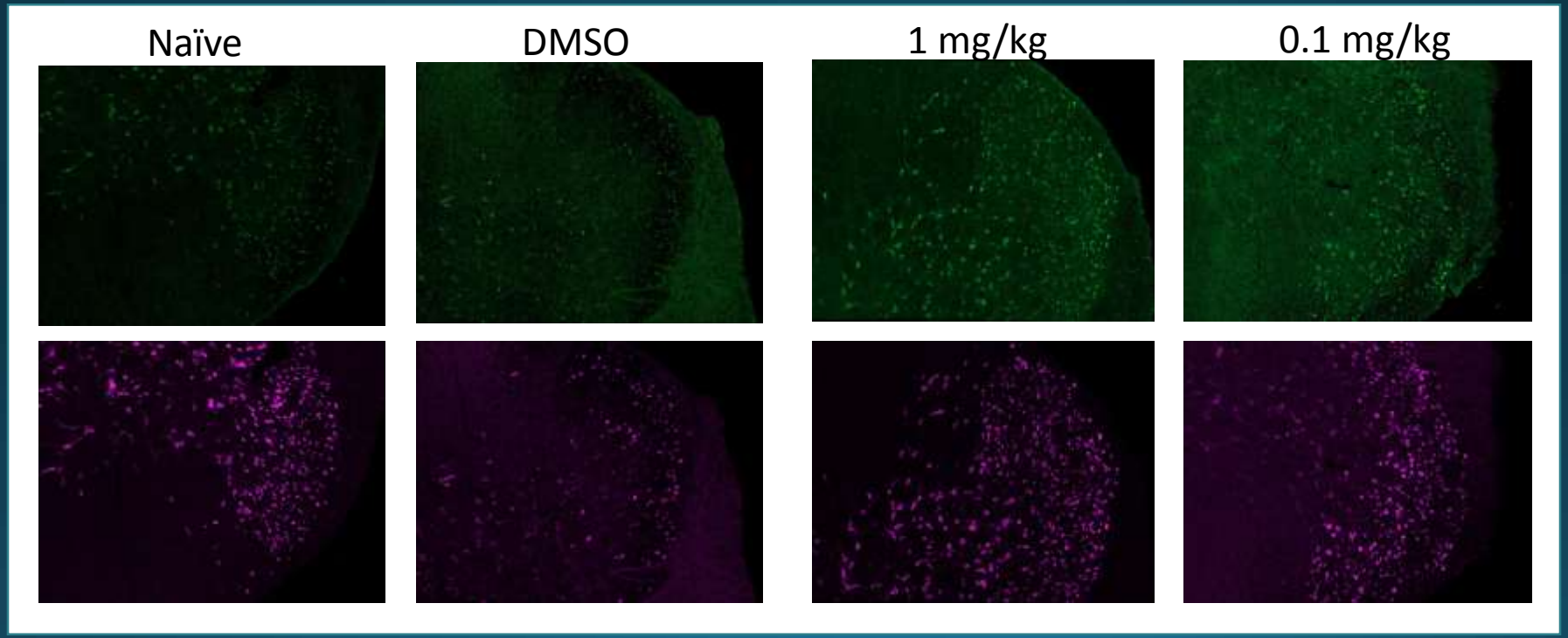
Green = MKP; Purple = DAPI staining of nucleus

CBD Stimulates Expression of MKP-2 in Dorsal Medullary Horn – 48 hr



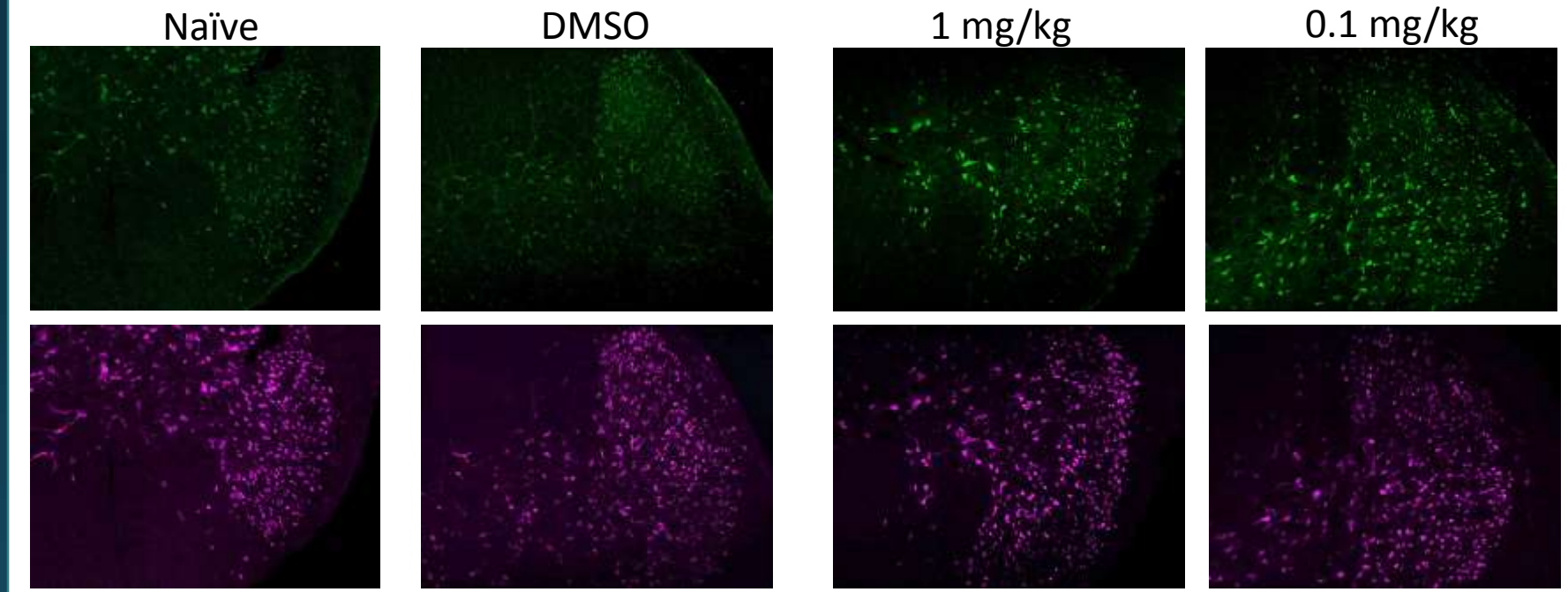
Green = MKP; Purple = DAPI staining of nucleus

CBD Increases Expression of MKP-3 in Dorsal Medullary Horn – 2 hr



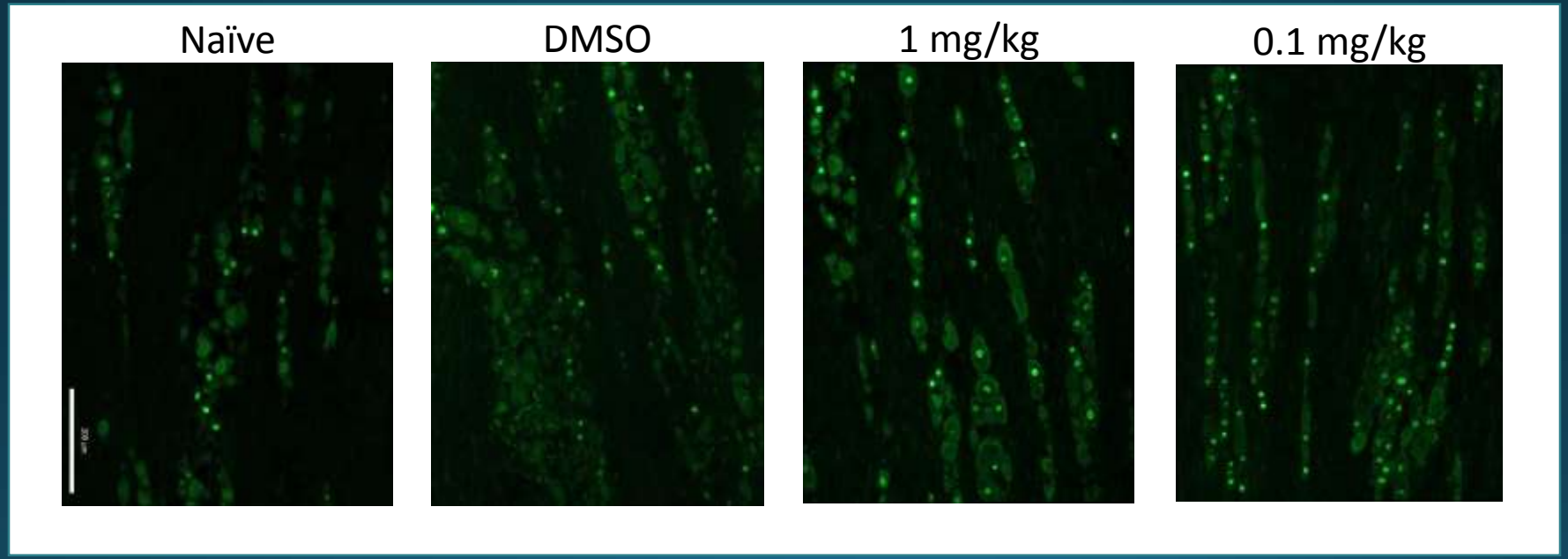
Green = MKP; Purple = DAPI staining of nucleus

CBD Increases Expression of MKP-3 in Dorsal Medullary Horn – 48 hr



Green = MKP; Purple = DAPI staining of nucleus

CBD Stimulated Expression of MKP-3 in Trigeminal Ganglion – 24 hr



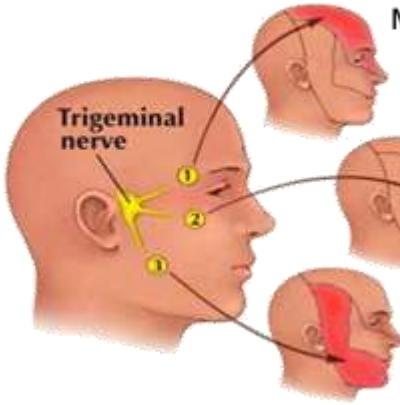
Green = MKP; Purple = DAPI staining of nucleus

Summary

- Treatment of animals with CBD enriched extract did not impair cognitive abilities such as novel object recognition and spatial reference memory.
- In agreement with our behavioral data, we did not observe significant changes in the levels of MKP-1, MKP-2, or MKP-3 in the region of the brain containing the hippocampus and dentate gyrus.
- CBD enriched extract had the greatest effect on MKP-2 and MKP-3 levels in the upper spinal cord tissue which contained the spinal trigeminal nucleus – the site where primary neurons that provide sensory innervation of the head and face synapse with second order nociceptive neurons.
- In the trigeminal ganglion, CBD extract caused an increase in MKP-3 expression in trigeminal neurons involved in pain transmission for up to 48 hrs.
- Generally, the lower concentration of CBD extract (0.1 mg/kg) mediated a similar cellular effect when compared to the higher concentration in stimulating MKP expression.

Conclusion

Trigeminal nerve activation is implicated in a number of inflammatory diseases including:



Migraine (V1 activation)

Rhinosinusitis (V2 activation)

Temporomandibular Joint Disorder (TMD; V3 activation)

Based on our results, we propose that CBD would be effective in blocking and potentially reversing pain mediated by either peripheral or central sensitization – physiological mechanisms implicated in migraine, TMD, and other neuroinflammatory diseases.

Pungent Odor
TRPA1 Receptors

California
Bay Leaf

Central Sensitization
Hyperalgesia/Allodynia

Cytokine and MAPK
Inflammatory Loop

Neuronal Cell Body

Satellite
Glia

Cytokine and MAPK
Inflammatory Loop

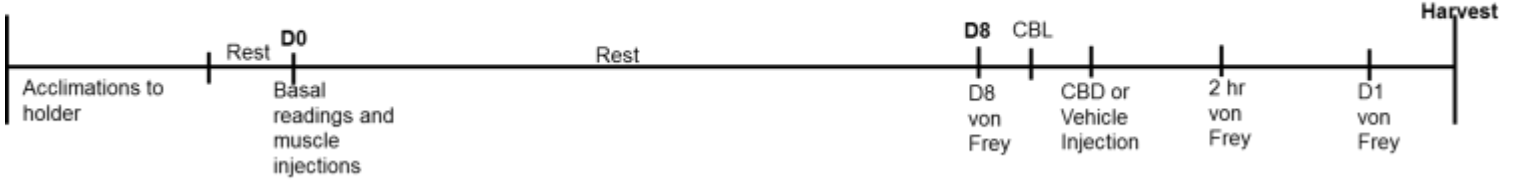
Sensitization
of Second Order
Neurons and Glia

STN

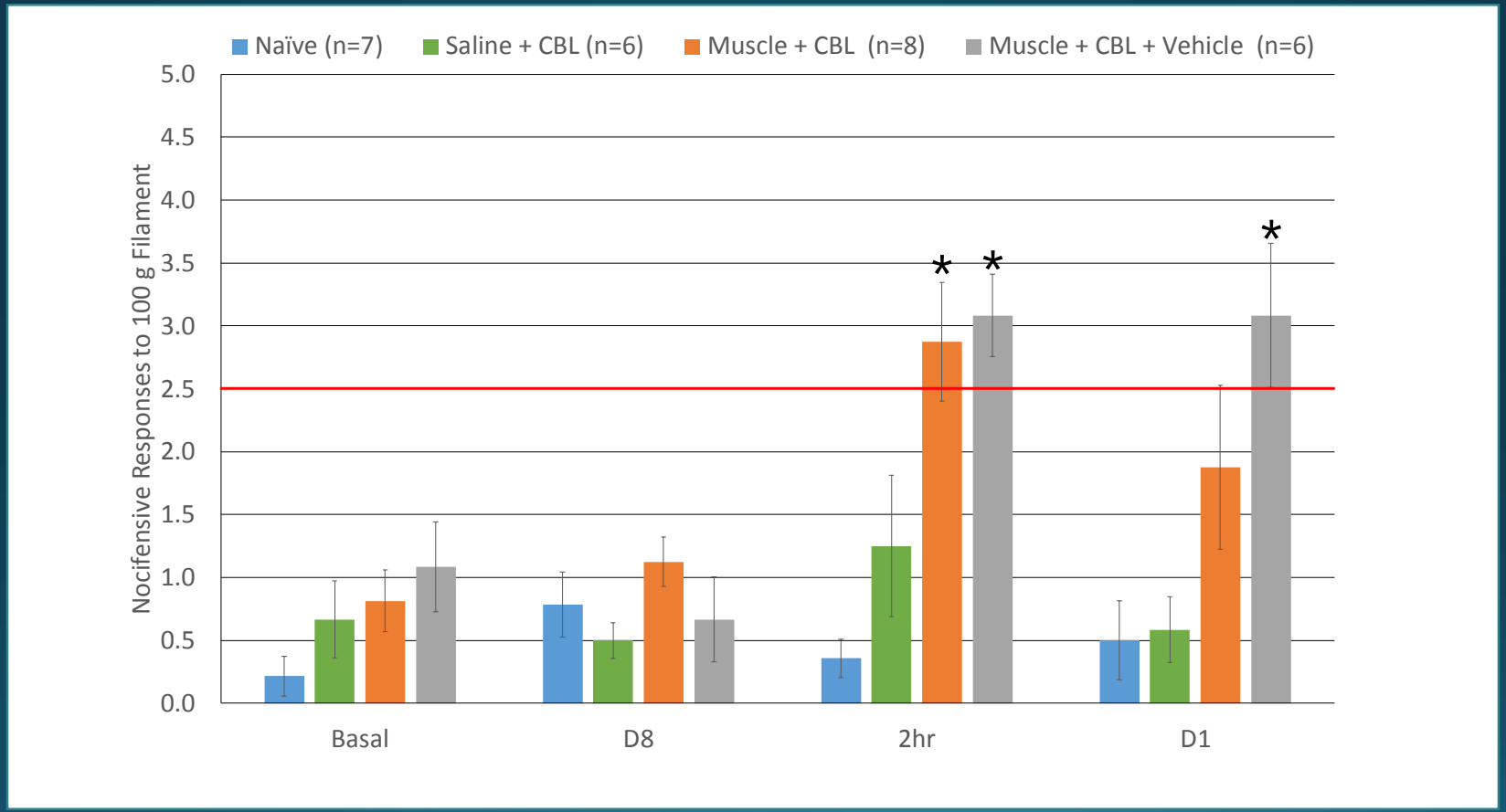
V1 and V2
Neurons

**Activation/Sensitization
of Primary Afferents**

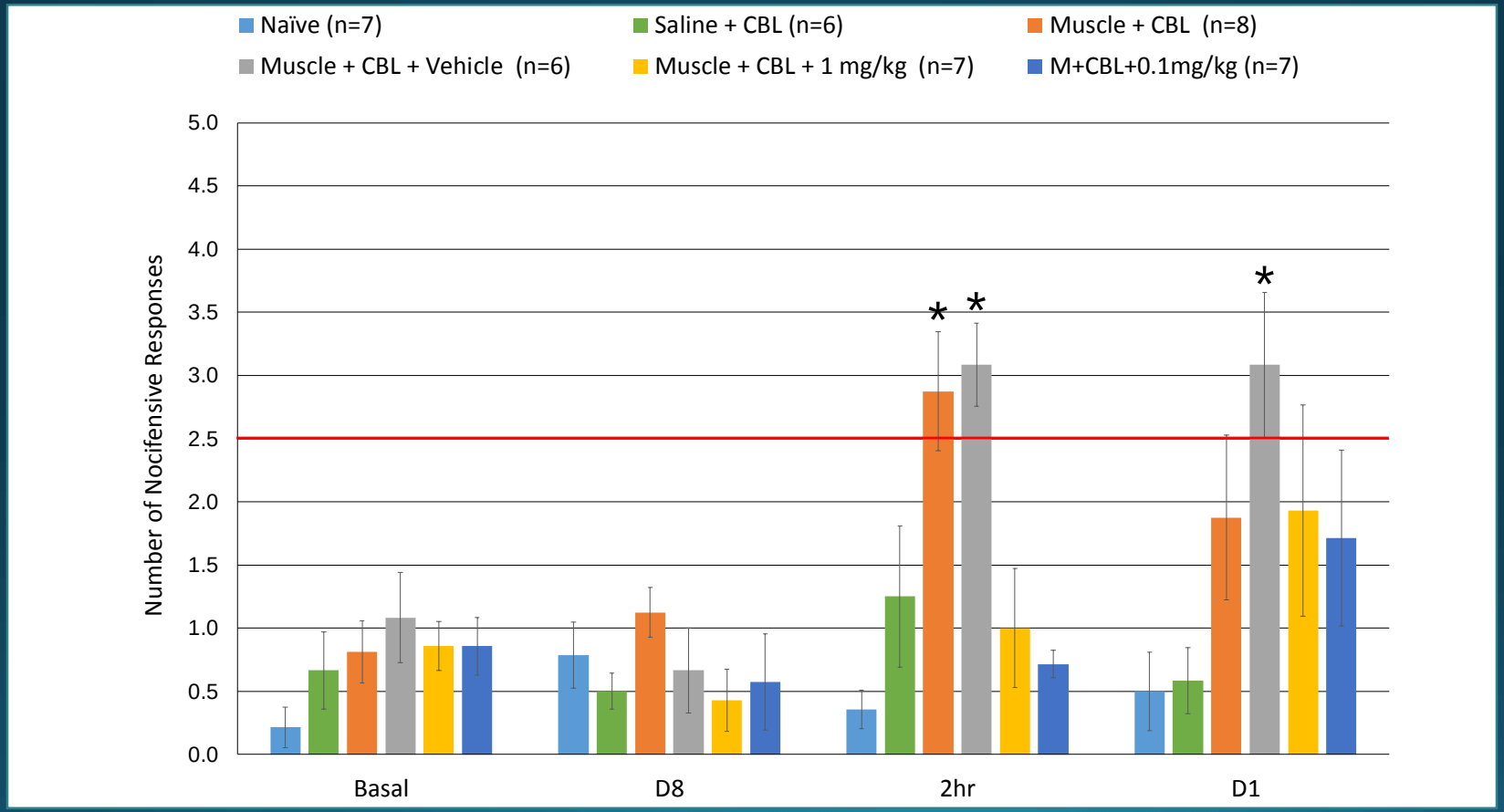
**Neck Muscle
Inflammation**



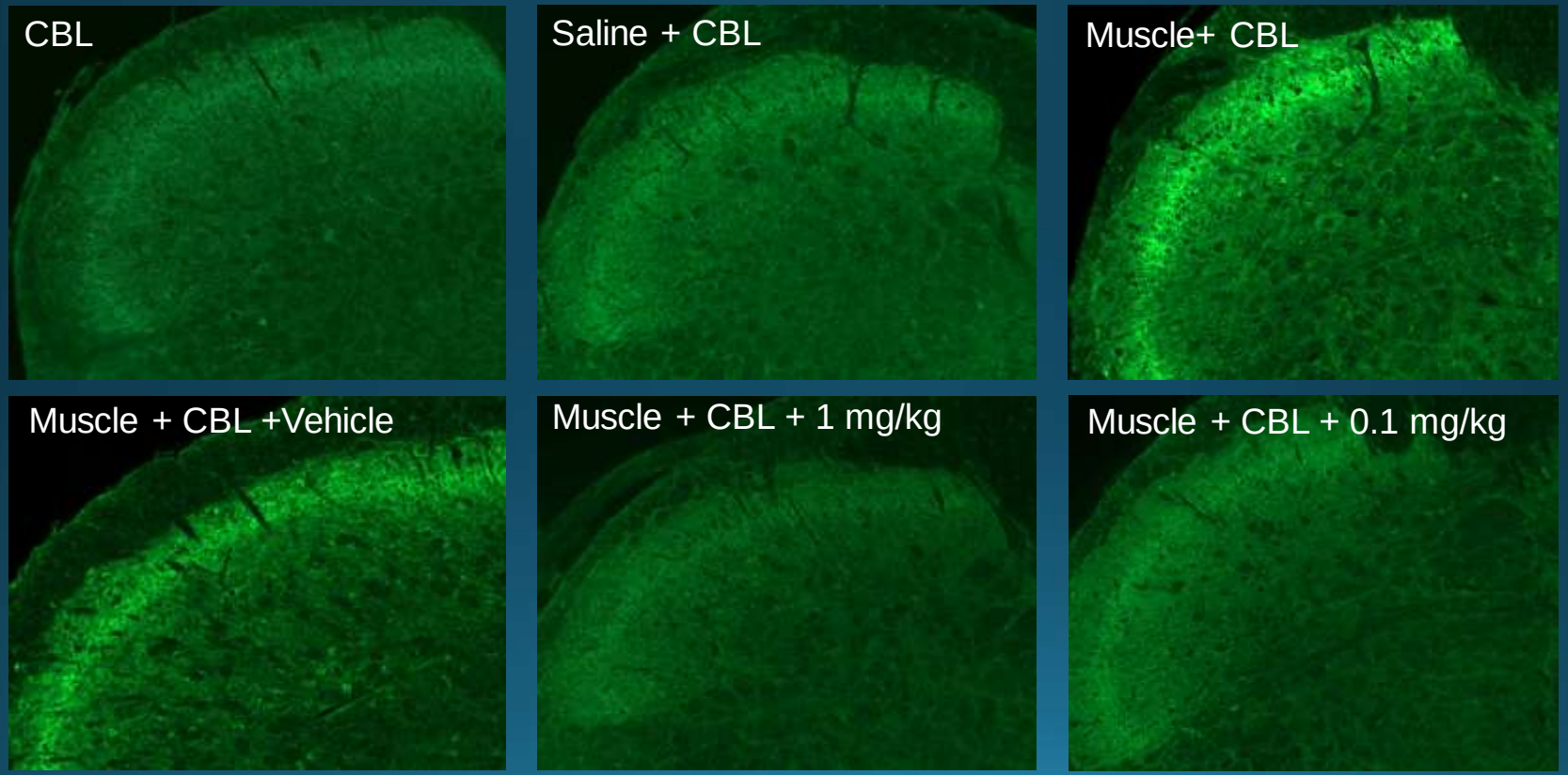
Exposure To a Pungent Odor Triggers a Transient Increase in Nocifensive Head Withdrawal Response to Mechanical Stimulation in Sensitized Animals



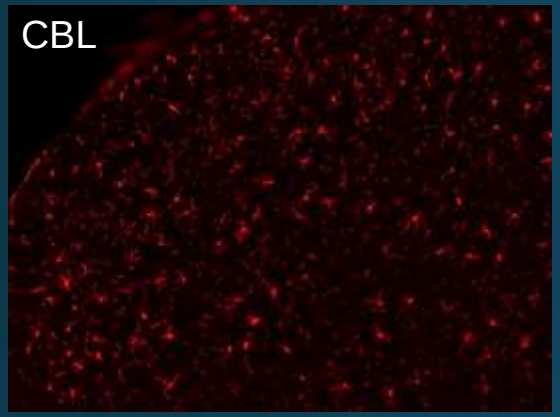
Cannabidiol Represses Trigeminal Nocifensive Responses Following Odorant Trigger in Sensitized Animals With Ongoing Neck Muscle Inflammation

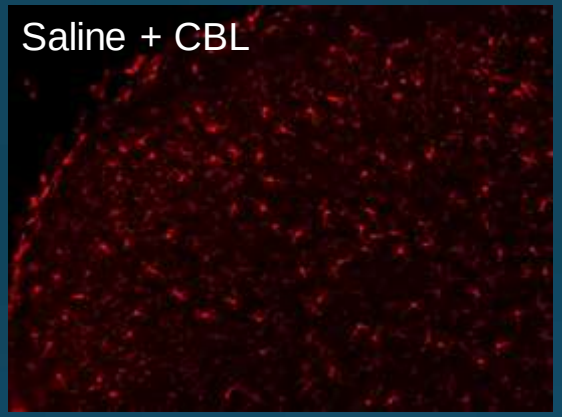


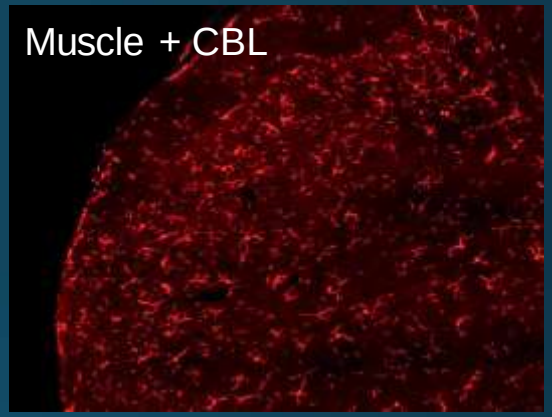
Cannabidiol Treatment Represses Increased PKA Expression in the Dorsal Medullary Horn Following California Bay Leaf Exposure In Sensitized Animals

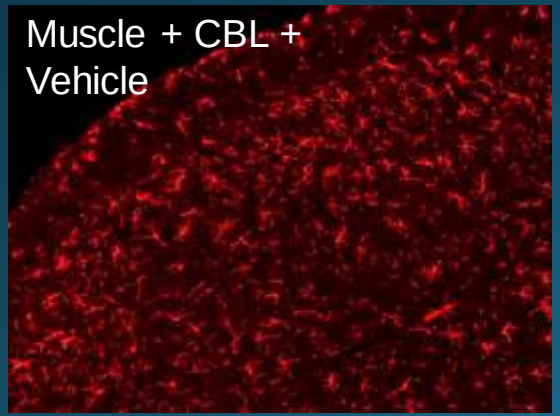


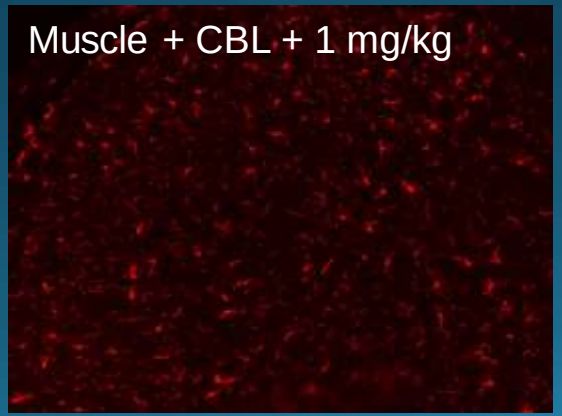
Cannabidiol Treatment Represses Increased Microglial Iba1 Expression in Sensitized Animals Following Exposure to California Bay Leaf Extract

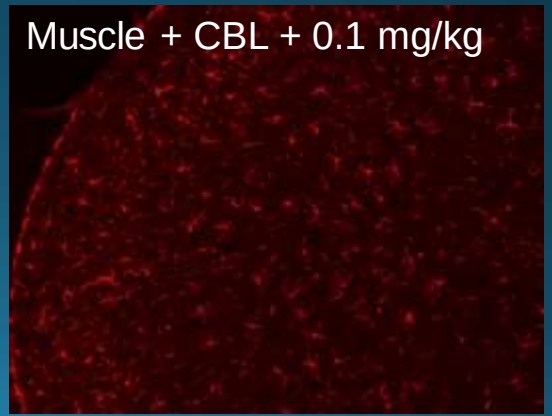










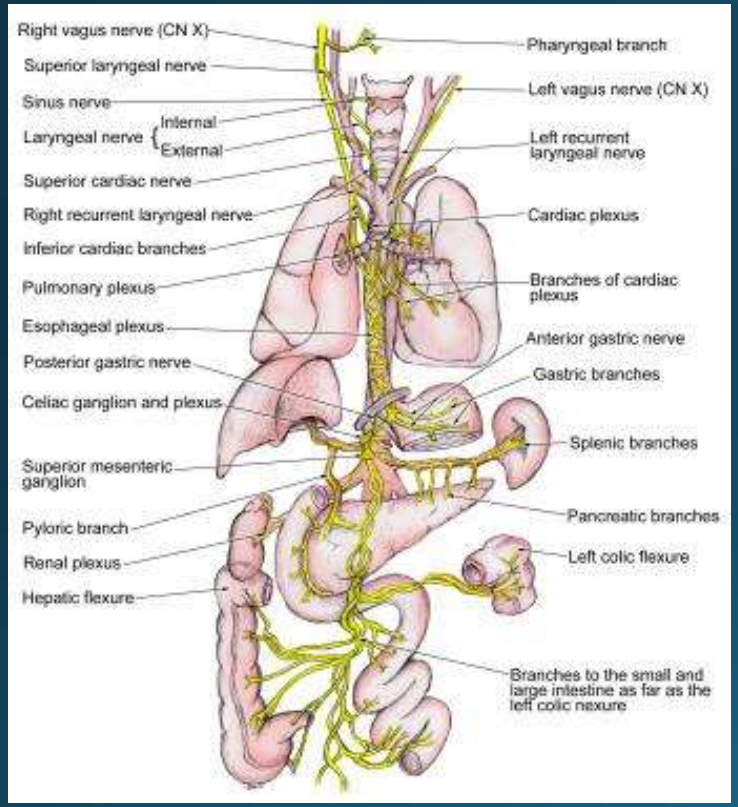


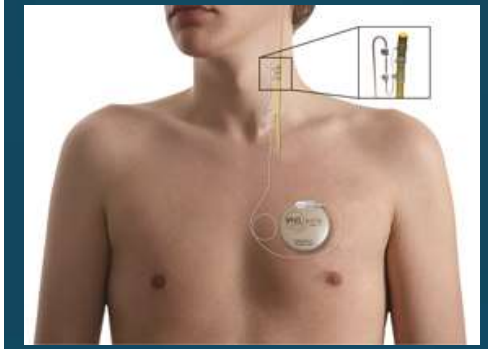
Non-Invasive Vagus Nerve Stimulation (nVNS)

- Inhibits Trigeminal Activation

- Represses Expression of Proteins Implicated in Central Sensitization

Vagus Nerve and Vagal Nerve Stimulation





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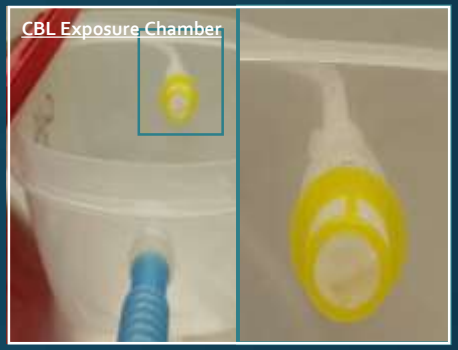
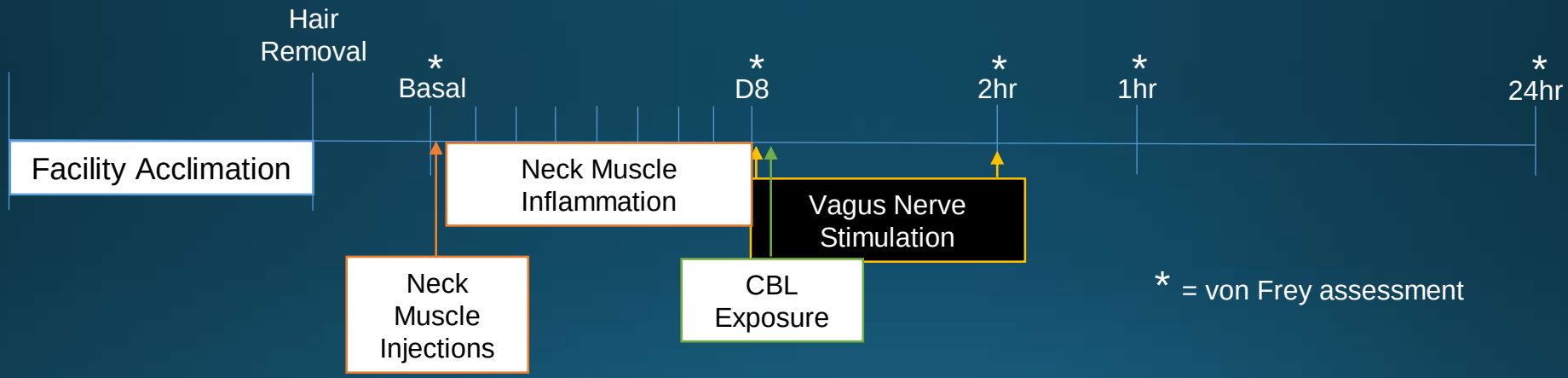
- Vagus Nerve -10th Cranial Nerve that contains both sensory and motor fibers
- Arises from numerous small roots from side of the medulla oblongata and supplies the pharynx, larynx, lungs, heart, esophagus, stomach, and most of the abdominal viscera
- Stimulation of the vagus nerve shown to be beneficial in depression, epilepsy, and migraine
- Vagal nerve stimulators - typically surgically implanted devices that generate electrical pulses to stimulate nerve
- Recently, transdermal vagus nerve stimulators have also shown efficacy in treating neurological pathologies, including migraine

Methods

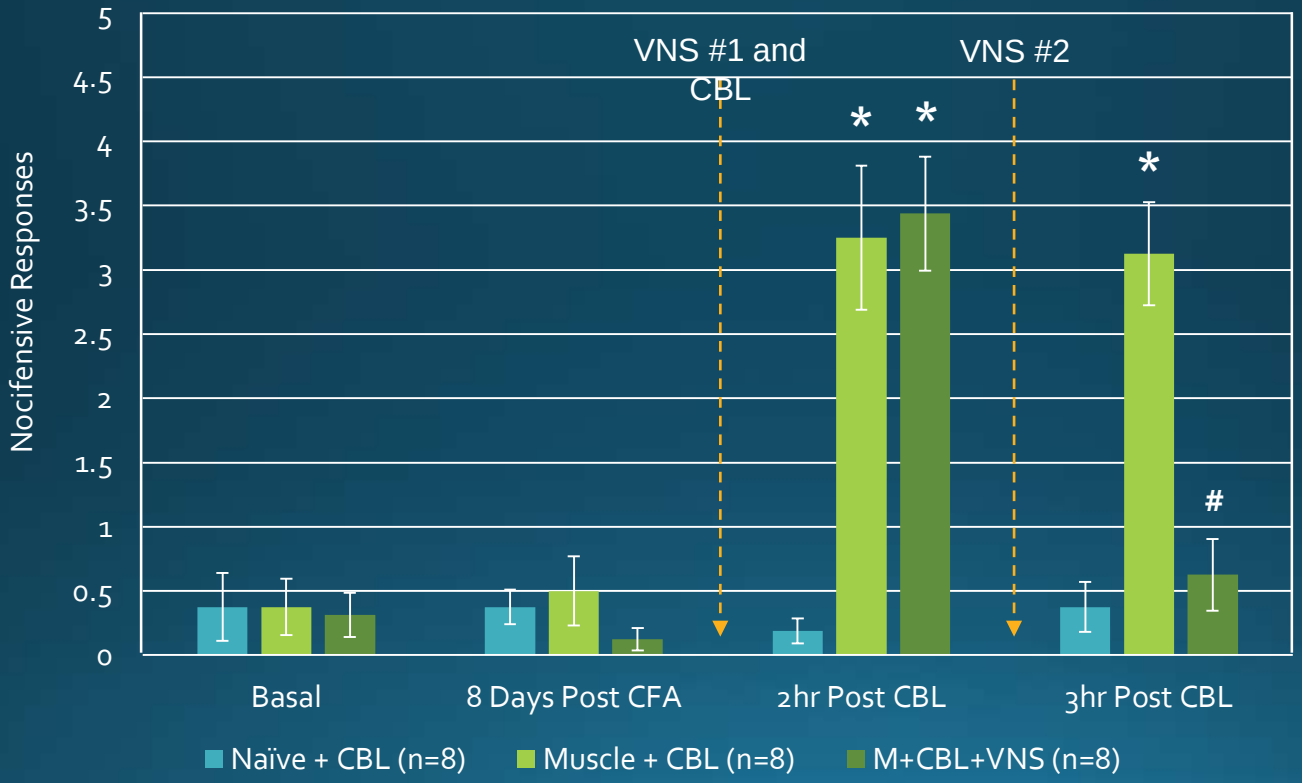
- Induction of Muscle Inflammation (Risk Factor)
  - Complete Freund's adjuvant (CFA)
- California Bay Leaf Oil Exposure (Trigger)
  - Oil extract from leaves of the *Umbellularia californica* tree that acts on TRPA1 receptors in the trigeminovascular system upon inhalation
- Vagus Nerve Stimulation
  - electroCore transdermal vagal nerve stimulator
- Mechanical Nociception
  - UGO Basile Durham Rat Holder and von Frey filaments



Experimental Outline: Treatment with VNS

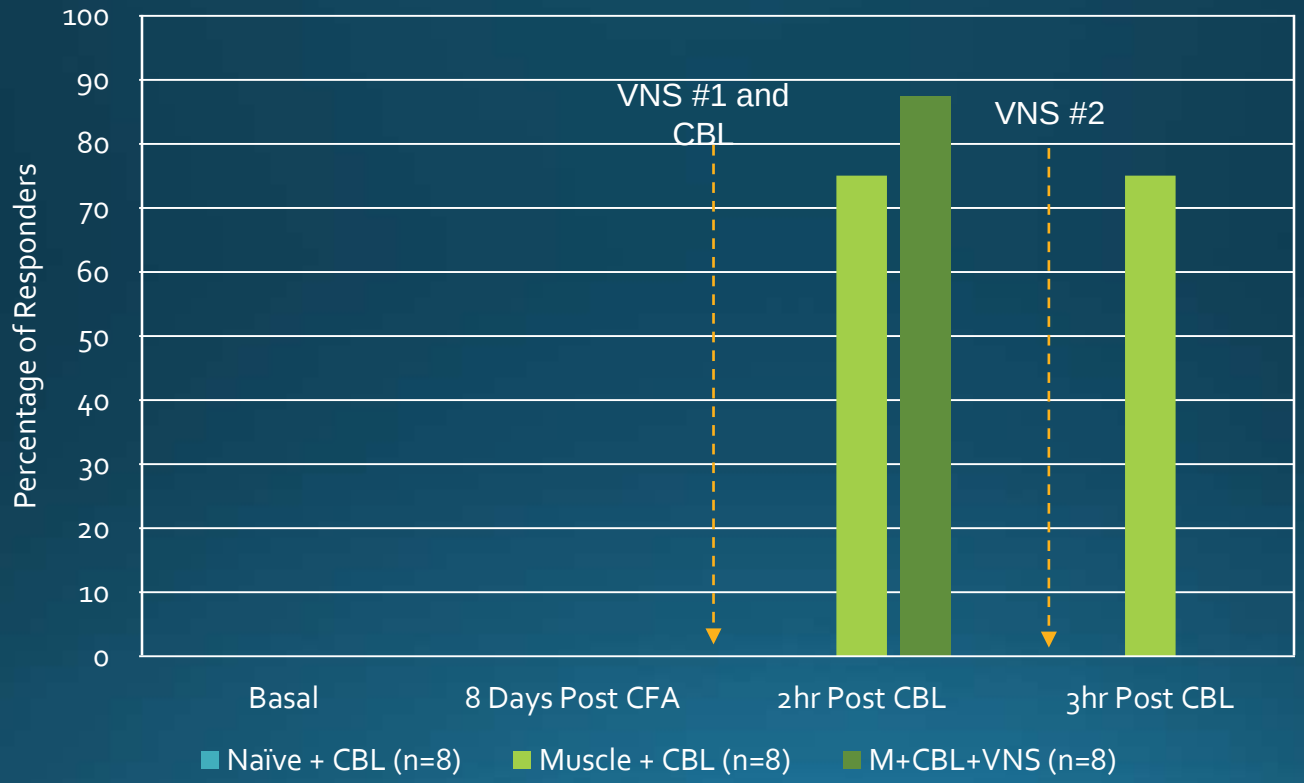


nVNS Inhibits Activation of Sensitized Trigeminal Nociceptors



Hawkins et al, Pain Reports, 2017

nVNS Inhibits Activation of Sensitized Trigeminal Nociceptors



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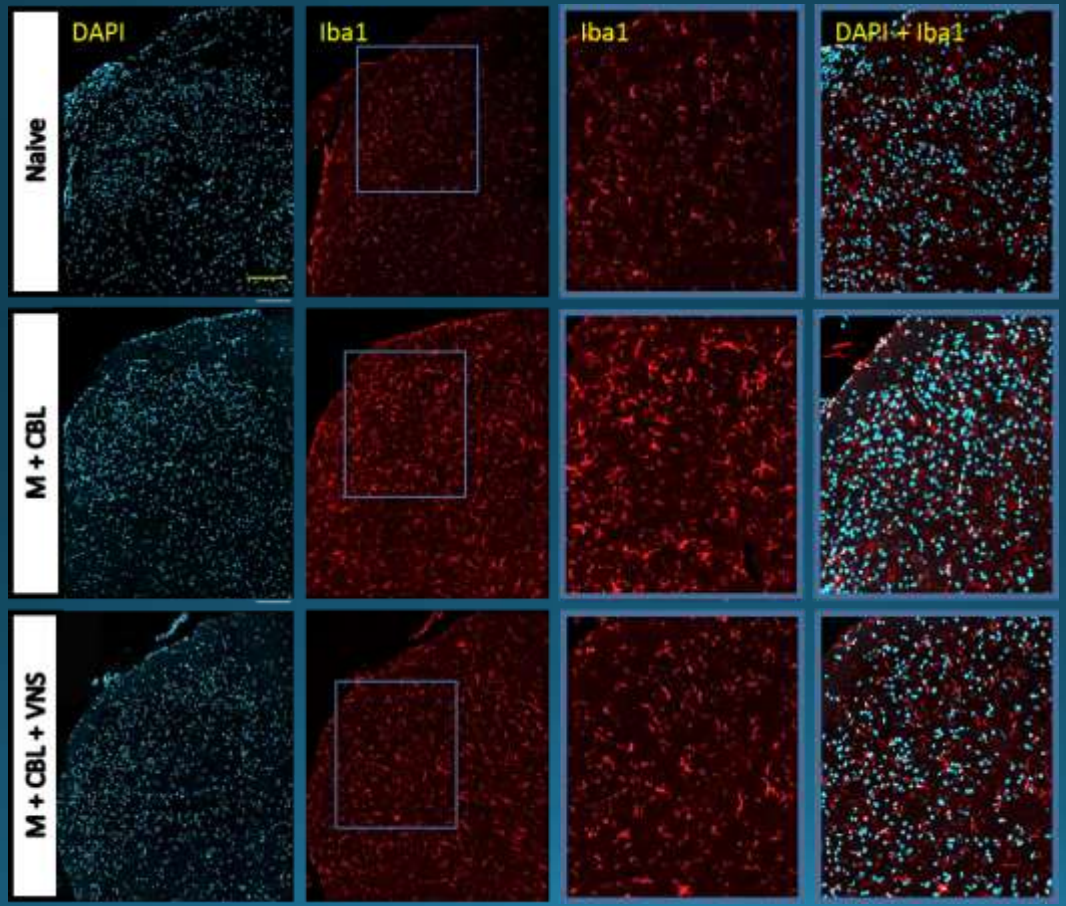
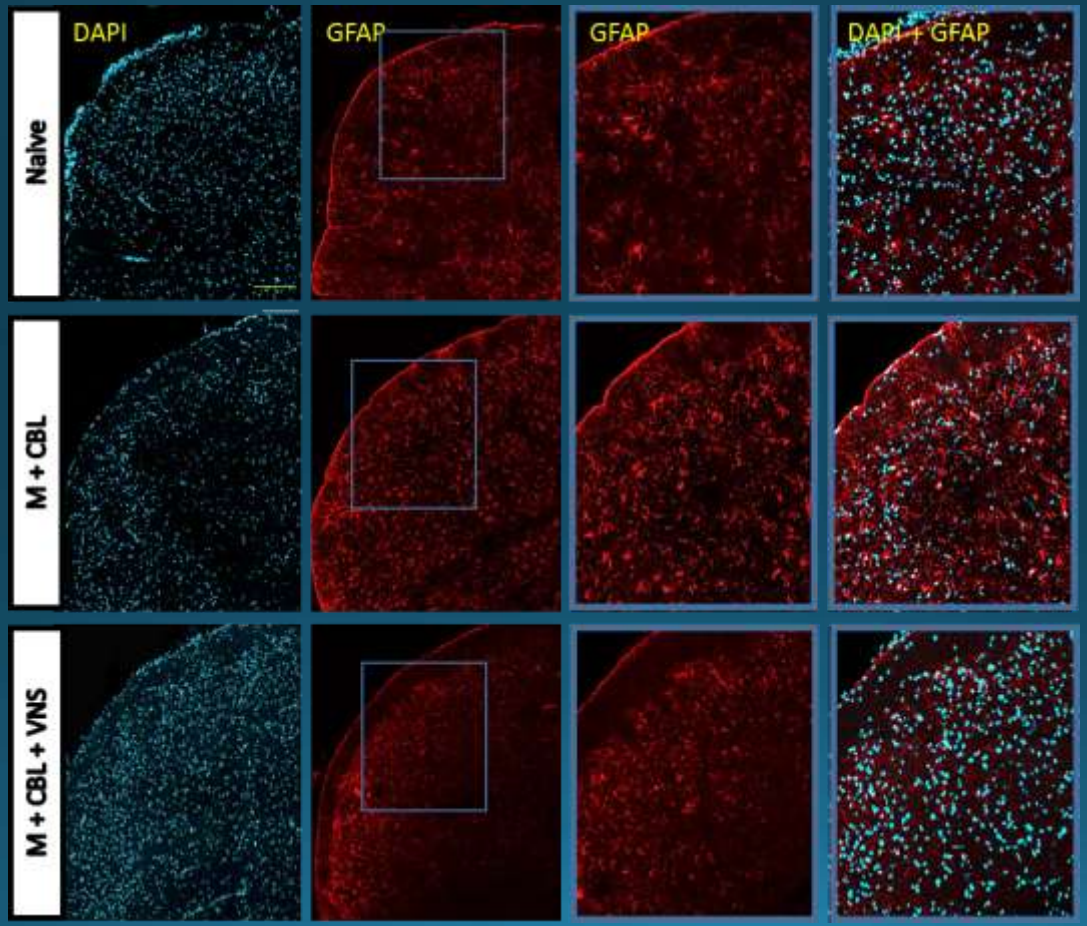
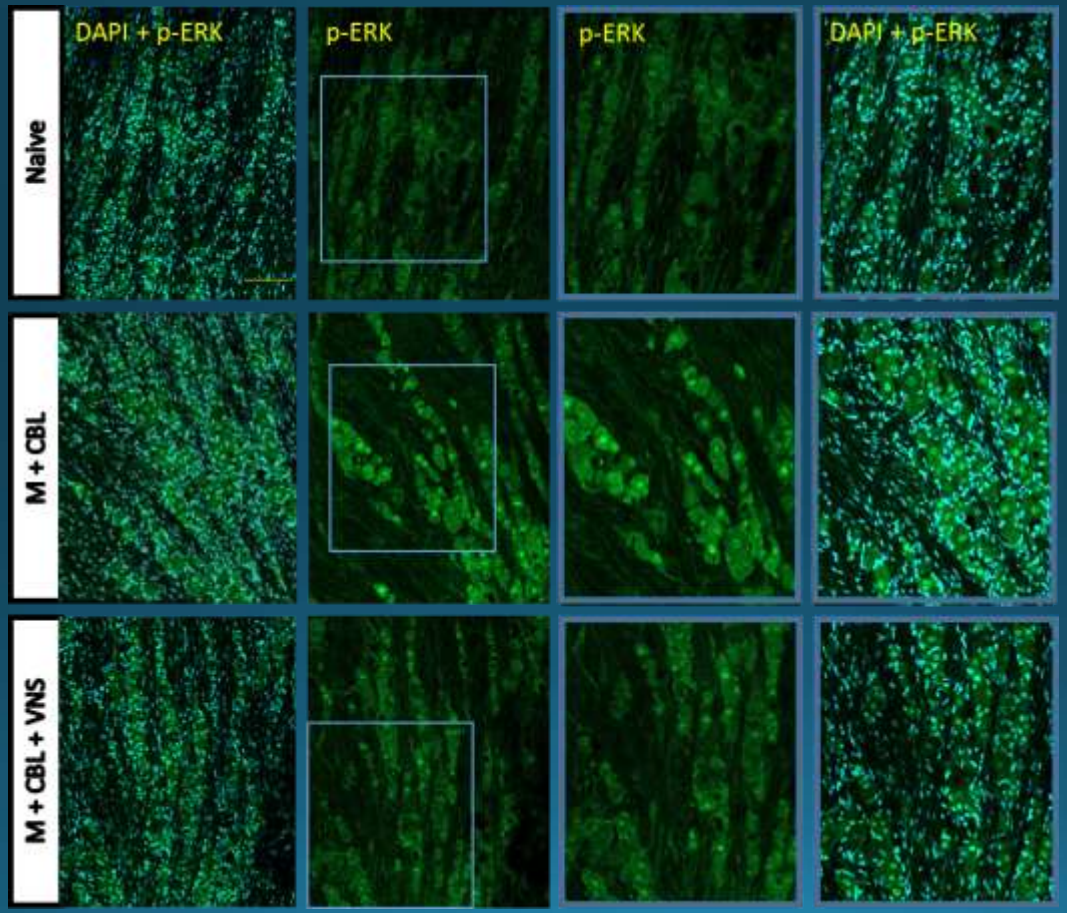
nVNS Inhibits Iba1 Microglial Expression in STN



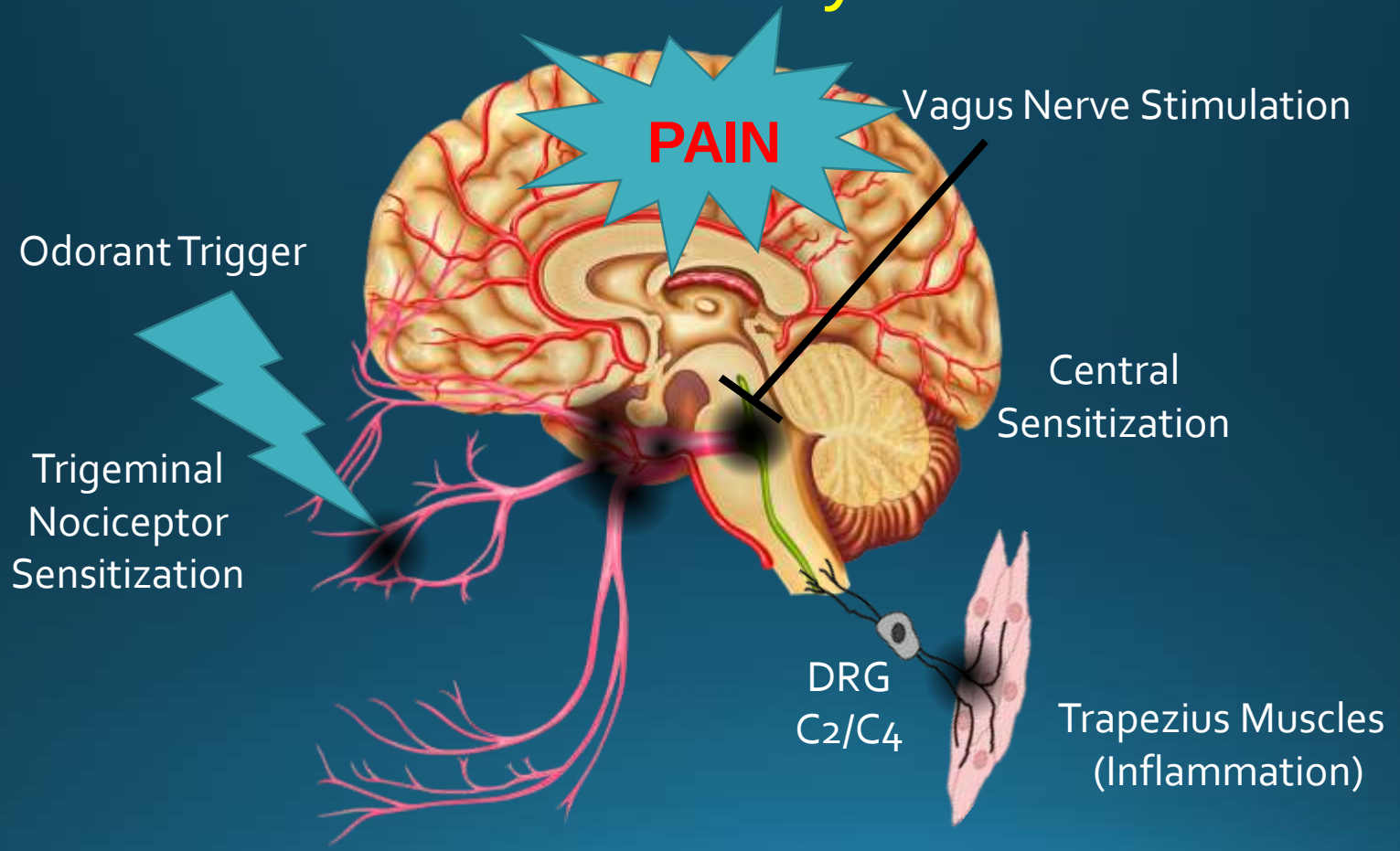
nVNS Inhibits GFAP Astrocyte Expression in STN



nVNS Inhibits P-ERK Expression in Trigeminal Ganglion



Summary



Hawkins et al, Pain Reports, 2017

Occlusal splint versus modified nociceptive trigeminal inhibition splint in bruxism therapy: a randomized, controlled trial using surface electromyography

B Dalewski,* M Chrusciel-Nogalska,* B Fraczak*

Australian Dental Journal 2015; 60: 445–454

Background: An occlusal splint and a modified nociceptive trigeminal inhibition splint (AMPS, anterior deprogrammer, Kois deprogrammer, Lucia jig, etc.) are commonly and quite frequently used in the treatment of masticatory muscle dis- orders, although their sustainable and long-lasting effect on these muscles' function is still not very well known. Results of scant surface electromyography studies in patients with temporomandibular disorders have been contradictory. The aim of this study was to evaluate both devices in bruxism therapy; EMG activity levels during postural activity and maximum voluntary contraction of the superficial temporal and masseter muscles were compared before and after 30 days of treatment.
Methods: Surface electromyography of the examined muscles was performed in two groups of bruxers (15 patients each). Patients in the first group used occlusal splints, while those in the second used modified nociceptive trigeminal inhibition splints. The trial was randomized, controlled and semi-blind.
Results: Neither device affected the asymmetry index or postural activity/maximum voluntary contraction ratio after 1 month of treatment.
Conclusions: Neither the occlusal nor the nociceptive trigeminal inhibition splint showed any significant influence on the examined muscles. Different scientific methods should be considered in clinical applications that require either direct influence on the muscles' bioelectrical activity or a quantitative measurement of the treatment quality.

Considering the SEMG approach and its normalization protocols, neither the occlusal nor the NTI splint showed any sustainable influence on the examined muscles after 1 month of typical bruxism treatment.

The role of the central nervous system in bruxism splint therapy requires further study.

Summary - Potential Novel Therapeutics for Orofacial Pain

- Grape Seed Extract
- Cocoa
- Cannabis – low THC expressing cultivars
- Vagal Nerve Stimulation
- Resveratrol – suppresses glial activation
- BOTOX – Botulinum toxin type A
- CGRP monoclonal antibodies

Inukshuk

"You are on the right path"

Goal of Health Care Professional:
Guide Patients Along Path to Good Health

SMILE

Regular Exercise

S
L
E
E
P

Good Relationships

D
I
E
T

Proper
Breathing