

Itch: From the Skin to the Brain – Peripheral and Central Neural Sensitization in Chronic Itch

Background

- Itch is an unpleasant sensory phenomenon that is encoded by histaminergic (in acute cases) and nonhistaminergic (in the majority of chronic cases) neuronal pathways
- Chronic itch is often associated with neural sensitization, which describes the process by which the nervous system experiences heightened sensitivity to stimuli.
- This process of neural sensitization of chronic itch is orchestrated by various signaling pathways and mediators in both the peripheral and central nervous systems.

Objective

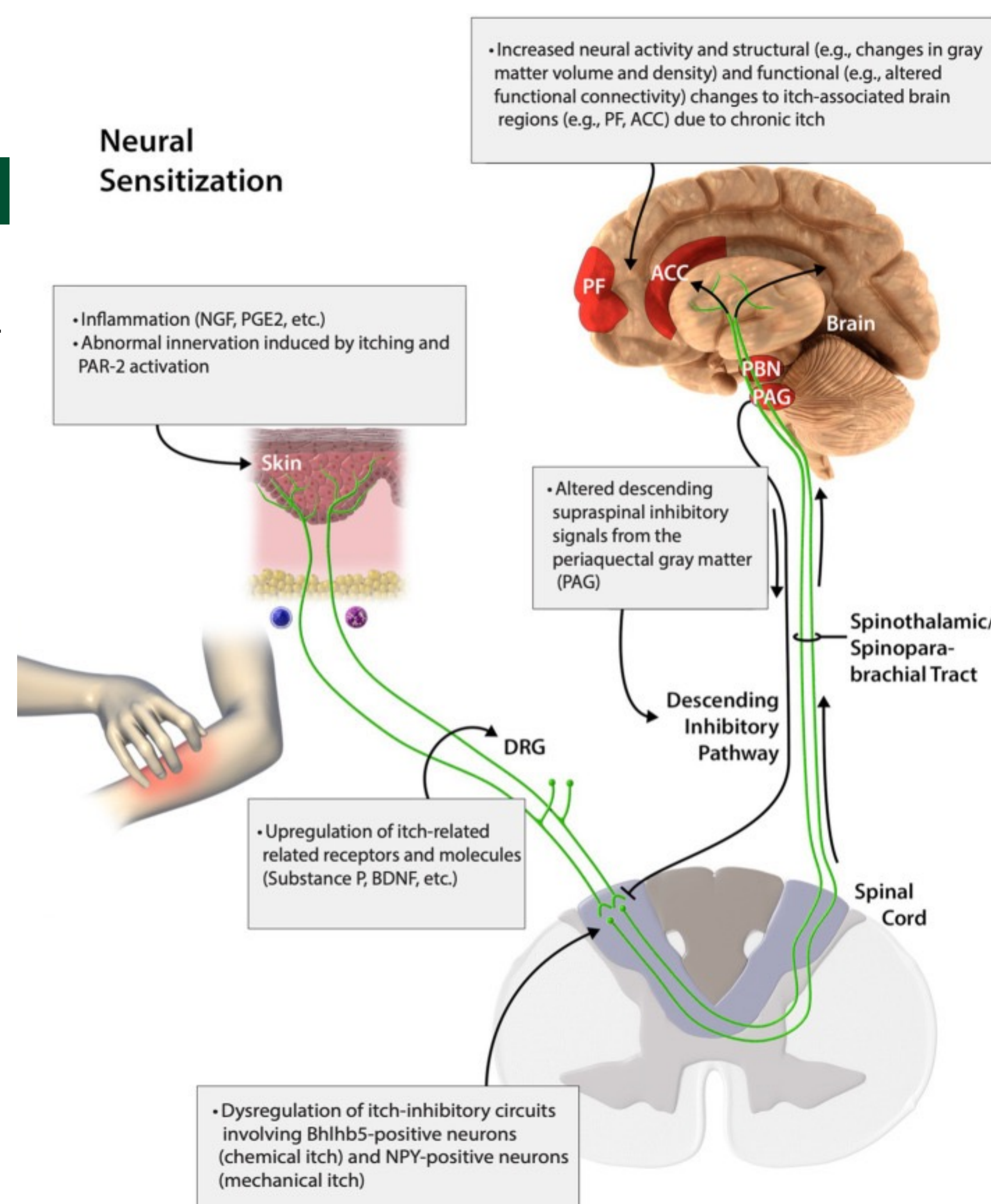
- To describe the peripheral and central mechanisms of the neural sensitization of itch and therapeutic options.

Peripheral Sensitization

- Peripheral sensitization occurs when a peripheral nerve undergoes increased response to pruritogens or algogens.
- In the skin, **inflammation**, **PAR-2 activation**, and **disordered innervation** induced by inflammation and scratching represent key mediators of sensitization, stimulating **upregulation of itch-related receptors and molecules** in the dorsal root ganglia².
- Various **itch-related channels and receptors** (i.e., Piezo channels, TRP channels, MRGPRs) as well as **immune mediators** (i.e., skin resident immune cells, neurotrophins, periostin, and phospholipase A2) are implicated.
- The cycle of itch mediator release from peripheral nerves, immune cells, and keratinocytes, as well as the transmission of itch signals, is responsible for the peripheral sensitization in chronic itch.

Central Sensitization

- Central neural sensitization in itch refers to the **abnormal amplification** and **dysregulation** of itch signals in the central nervous system (CNS), which includes the brain and spinal cord, resulting in **heightened responsiveness and sensitivity to itch stimuli**.
- In the spinal cord, **dysfunction of inhibitory circuits** including neuropeptide Y and Bhlhb-5 neurons, as well as **attenuation of descending, inhibitory pathways** are at play.
- In the brain, neural sensitization is associated with **structural and functional changes to itch-associated brain areas and networks** (i.e., prefrontal area, anterior cingulate cortex).



Mahmoud O, Oladipo O, Mahmoud RH, Yosipovitch G. Itch: from the skin to the brain - peripheral and central neural sensitization in chronic itch. *Front Mol Neurosci*. 2023 Oct 2;16:1272230. doi: 10.3389/fnmol.2023.1272230. PMID: 37849619; PMCID: PMC10577434.

Therapeutics

GABAergic Drugs	Increase GABA inhibitory neurotransmission in the CNS and decrease the release of peripheral substance P and calcitonin gene-related peptide from primary afferent neurons by increasing spinal cord GABA.
Kappa Opioids	Correct imbalance in endogenous opioid system to help reduce itch sensitization in the CNS.
Immunomodulatory Therapies (e.g., Dupilumab, Nemolizumab, JAK Inhibitors)	Decrease the effect of itch-promoting cytokines IL-4, IL-13, and IL-31 on peripheral itch-conveying sensory nerve fibers, thereby reducing peripheral sensitization.
NMDA Receptor Targets (e.g., Ketamine)	Inhibit NMDA-dependent excitatory signaling in the periphery (topical application) and centrally (intravenous or inhaled formulations); central-acting formulations may reduce central sensitization by attenuating neural plasticity.
Antioxidant Flavonoids	Antioxidant (neutralize free radicals and reactive oxygen species) and anti-inflammatory (decrease pro-inflammatory cytokines and chemokines) effects.
Cognitive Behavioral Therapy	Decrease stress, maladaptive thoughts, and scratching behaviors leading to reduced itch and affecting brain structure and function.
Transcranial Magnetic Stimulation	Modulate neural activity of brain regions via application of a weak magnetic field through the scalp.

Conclusion

- Neural sensitization in the context of chronic itch is orchestrated by various signaling pathways and mediators in both the peripheral and central nervous systems.
- Further research is needed to expand our understanding and therapeutic repertoire.

References

1. Mahmoud O, Oladipo O, Mahmoud R. H., & Yosipovitch, G. (2023). Itch: from the skin to the brain - peripheral and central neural sensitization in chronic itch. *Frontiers in molecular neuroscience*, 16, 1272230.
2. Yosipovitch G., Rosen J. D., Hashimoto T. (2018). Itch: from mechanism to (novel) therapeutic approaches. *J. Allergy Clin. Immunol.* 142, 1375–1390.