Publication News 113 – 11 March 2024

The role of dietary lipids and acid-sensing ion channel 3 in obesity-induced painful neuropathy

***Aims*:** The aim of the current work was to examine the mechanisms underlying pain perception secondary to obesity and prediabetes in dorsal root ganglia (DRG) neurons. The authors proposed that excess dietary lipids, by interacting with acid-sensing ion channel 3 (*Asic3*), a neuronal voltage-insensitive sodium channel, increase nociceptor sensitization and mediate pain hypersensitivity.
***Methods*:** The metabolic phenotype and pain behavior were assessed in a high-fat fed mouse model. The authors also carried out lipidomics on high-fat diet animals serum to identify what lipotoxic species are interacting with *Asic3*. Next, a combination of primary DRG cultures, single-cell recording, and patch clamp technique characterized neuronal hyperexcitability in the presence or absence of excess dietary lipids. Finally, genetic and pharmacologic inhibition of *Asic3* determined its direct role in obesity-induced thermal hyperalgesia.
***Results*:** As expected, high-fat diet animals developed obesity and prediabetes, with impaired glucose tolerance, insulin resistance, and dyslipidemia. These metabolic abnormalities were accompanied with thermal hyperalgesia. Serum from high-fat fed mice contained high lipid concentrations, including phosphatidylcholine and lysophosphatidylcholine species which were found to sensitize and depolarize small and medium diameter DRG neurons, by activating *Asic3* using the patch-clamp approach. While *Asic3* genetic or pharmacological inhibition did not impact metabolic parameters in high-fat fed mice, it restored thermal sensation.
***Conclusions*:** Together, these findings suggest that excess dietary lipids can activate *Asic3* resulting in sensory neuron hyperexcitability and thermal pain in obese, prediabetic mice.

Comments. The global epidemic of obesity and prediabetes has led to a corresponding epidemic of their complications, including peripheral neuropathy, which represents an immense clinical problem in the realm of neurological disorders. Peripheral neuropathy results in a range of debilitating symptoms such as numbness, tingling, weakness, as well as burning or shooting pain. Along with these painful symptoms, patients may experience depression, anxiety, and sleep disturbances. With disease progression, individuals may present with diminished sensation to mechanical and/or thermal stimuli, making it challenging to perceive injuries or trauma and increasing the risk of non-healing ulcers and lower-limb amputations. Despite the enormity of the problem, treatment options are still limited due in part to our incomplete understanding of disease pathogenesis. This work reveals that excess dietary lipids can directly sensitize and depolarize sensory afferent neurons through their action on *Asic3*, a neuronal voltage-insensitive sodium channel, which is implicated in acute, inflammatory, neuropathic, visceral and cancer pain. Importantly, *Asic3* genetic or pharmacologic inhibition effectively restores thermal sensation, providing a meaningful therapeutic target for the treatment of painful neuropathy. Beyond that, these findings reinforce the increasing preclinical and clinical evidence linking unhealthy dietary fats to peripheral nerve damage.

Stéphanie Eid

Reference. Negm A, Stobbe K, Ben Fradj S, Sanchez C, Landra-Willm A, Richter M, Fleuriot L, Debayle D, Deval E, Lingueglia E, Rovere C, Noel J. Acid-sensing ion channel 3 mediates pain hypersensitivity associated with high-fat diet consumption in mice. Pain. 2024 Feb 1;165(2):470-486. doi: 10.1097/j.pain.0000000000003030. PMID: 37733484.
https://journals.lww.com/pain/fulltext/2024/02000/acid_sensing_ion_channel_3_mediates_pain.22.aspx