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Methylglyoxal modification of Nav1.8 facilitates nociceptive neuron firing and causes hyperalgesia in diabetic neuropathy.

Bierhaus A[1], Fleming T, Stoyanov S, Leffler A, Babes A, Neacsu C, Sauer SK, Eberhardt M, Schnölzer M, Lasitschka F, Neuhuber WL, Kichko TI, Konrade I, Elvert R, Mier W, Pirags V, Lukic IK, Morcos M, Dehmer T, Rabbani N, Thornalley PJ, Edelstein D, Nau C, Forbes J, Humpert PM, Schwaninger M, Ziegler D, Stern DM, Cooper ME, Haberkorn U, Brownlee M, Reeh PW, Nawroth PP.

Author information

Erratum in

Nat Med. 2012 Sep;18(9):1445. Lasischka, Felix [corrected to Lasitschka, Felix].

Abstract

This study establishes a mechanism for metabolic hyperalgesia based on the glycolytic metabolite methylglyoxal. We found that concentrations of plasma methylglyoxal above 600 nM discriminate between diabetes-affected individuals with pain and those without pain. Methylglyoxal depolarizes sensory neurons and induces post-translational modifications of the voltage-gated sodium channel Na(v)1.8, which are associated with increased electrical excitability and facilitated firing of nociceptive neurons, whereas it promotes the slow inactivation of Na(v)1.7. In mice, treatment with methylglyoxal reduces nerve conduction velocity, facilitates neurosecretion of calcitonin gene-related peptide, increases cyclooxygenase-2 (COX-2) expression and evokes thermal and mechanical hyperalgesia. This hyperalgesia is reflected by increased blood flow in brain regions that are involved in pain processing. We also found similar changes in streptozotocin-induced and genetic mouse models of diabetes but not in Na(v)1.8 knockout (Scn10(-/-)) mice. Several strategies that include a methylglyoxal scavenger are effective in reducing methylglyoxal- and diabetes-induced hyperalgesia. This previously undescribed concept of metabolically driven hyperalgesia provides a new basis for the design of therapeutic interventions for painful diabetic neuropathy.

Comment in

Diabetes: Methylglyoxal mediates hyperalgesia in patients with painful diabetic neuropathy. [Nat Rev Neurol. 2012]

Ion channels: Metabolite targets sodium channels in diabetic pain. [Nat Rev Neurosci. 2012]

PS: pain and sodium channels. [Clin Genet. 2012]

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