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- EDITORS' CHOICE

PAIN

A Painful Question of Metabolism

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The treatment of neuropathic pain is a major challenge for clinicians. There are many different mechanisms by which pain can be provoked, but for some patients a specific cause is tough to identify. The quest to identify mechanisms involved in neuropathic pain will be crucial for the development of new treatment options. In a new study, Patti and colleagues propose that the endogenous metabolite N,N-dimethylsphingosine (DMS) induces mechanical allodynia, a principal feature of neuropathic pain in which stimuli usually perceived as not painful provoke a fulminant pain response.

First, Patti and coworkers performed an untargeted metabolomics screen in a rat model of neuropathic pain. They obtained ~700 dysregulated metabolites that showed a greater-than-twofold increase as compared with control animals. These metabolites were localized predominantly to the ipsilateral dorsal horn of the spinal cord. By relating the metabolomics signature to the pain phenotype, the authors were able to identify a cluster of alterations in sphingomyelin-ceramide metabolism. They were particularly intrigued by up-regulation of the sphingolipid DMS. They demonstrated that intrathecal administration of DMS to control rats elicited mechanical allodynia. They then treated astrocytes in culture with DMS and found that DMS induced the release of interleukin-1β and monocyte chemoattractant protein-1, inflammatory mediators known to be involved in pain perception.

This study exemplifies the value of metabolomics analysis in the challenging field of neuropathic pain research. The next step will be to explore in greater detail the regulation and action of DMS in vivo and eventually to test the relevance of this metabolite to neuropathic pain in humans.

G. J. Patti *et al.*, Metabolomics implicates altered sphingolipids in chronic pain of neuropathic origin. *Nat. Chem. Biol.* **8**, 232–234 (2012). [PubMed]

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