A Novel Sphingomyelin Metabolite Involved in Chronic Pain

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Importance for Chiari patients

Chronic pain is a common and debilitating symptom for individuals with Chiari malformation and syringomyelia. Current treatments for chronic pain have significant side effects and are not effective for all patients. A fuller understanding of the pathogenic mechanisms that lead to pain in Chiari are essential to facilitate the development of improved analgesics.

Abstract

Chiari malformation is a group of disorders characterized by herniation of the cerebellum through the foramen magnum of the skull that may also be accompanied by syringomyelia, the formation of a cyst or cavity within the spinal column. A prominent symptom of this disorder is chronic pain, the pathogenic mechanisms of which are not well-understood. Recently, we characterized alterations in sphingomyelin metabolism within the spinal cord that are associated with the development of chronic pain. This project seeks to examine how dysregulation of sphingomyelin metabolism contributes to the development of pain during Chiari by using mass spectrometry. Understanding pain-specific biochemical alterations will facilitate the development of more effective analgesics to treat chronic pain and significantly improve the quality of life for patients.

Introduction

Metabolomics is a new technology that provides a global view of cellular metabolism. Using mass spectrometry, it is possible to profile small molecule metabolites which collectively comprise the metabolome. An untargeted metabolomic screen was performed on a small animal model of neuropathic pain to identify biochemical alterations associated with the development of allodynia1. Significant metabolite alterations were detected in the spinal cord, including changes in the levels of sphingomyelins, a class of membrane lipids that function as precursors for important signaling molecules. We identified the sphingomyelin metabolite, N,N-dimethylsphingosine (DMS), as a key molecule involved in promoting inflammatory responses in the central nervous system (CNS) during pain. Furthermore, DMS is also upregulated in the CNS of human patients during white matter injury. Therefore, the goal of this project is to examine the contribution of DMS in promoting abnormal pain responses and pathogenic changes in CNS tissue during Chiari and syringomyelia.

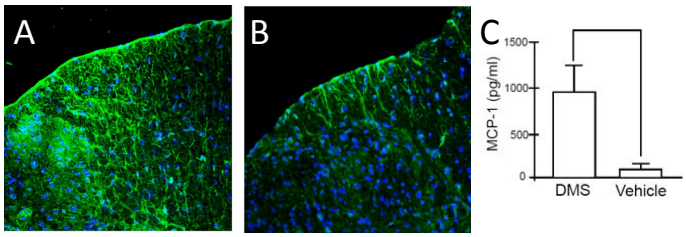

Figure 1. DMS injection induces pain-related pathology in the spinal cord. Following intrathecal inoculation of DMS, spinal cord tissue was collected and stained for astrocyte pathology using an antibody against GFAP. A) A confocal image from a DMS-treated animal showing increased GFAP staining in the dorsal horn compared to a vehicle-treated animal (B). C) DMS treatment of cultured astrocytes induces release of an inflammatory chemokine MCP-1 that promotes neuronal hypersensitivity.

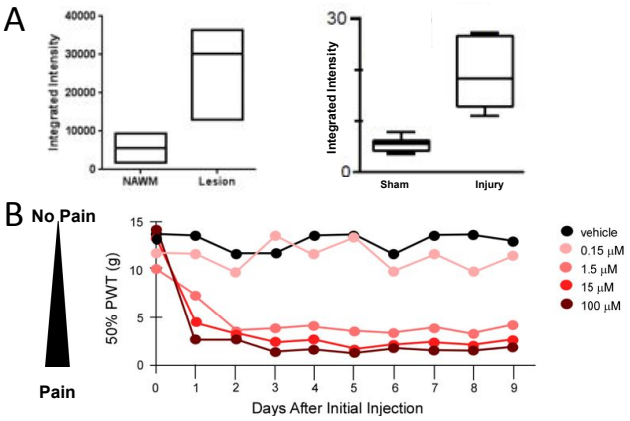

Figure 1. Increased DMS production in the CNS is associated with pain and white matter injury. A) Metabolomic analysis showing increased DMS production in an animal model of chronic pain and in human tissue after CNS injury. B) Injection of DMS induces pain responses in rats.

Methods

DMS Detection. Mass spectrometry was used to profile rat spinal cord tissue after tibial nerve transection as well as in brain tissue isolated from patients with inflammatory white matter damage.

In Vivo Analysis of DMS. DMS was administered to via intrathecal injection at increasing concentrations and the development of mechanical allodynia was determined with Von Frey filaments. Immunohistochemistry for GFAP was performed on isolated spinal cord and DMS production by astrocytes was determined using ELISA.

Results and Discussion

DMS production in the spinal cord was associated with the development of chronic pain, astrocyte reactivity, and production of inflammatory mediators known to induce neuronal hypersensitivity. Furthermore, DMS is significantly upregulated in CNS tissue taken from patients with white matter injury. Taken together, these results suggest that injury to the CNS, such as that which occurs during syringomyelia, could result in abnormal production of the signaling lipid, DMS. Future work will track production of DMS in CSF isolated from Chiari patients as well as identify the new inhibitors of DMS production that could prevent the development of pain after CNS injury.

Conclusions

- Altered sphingomyelin metabolism is associated with chronic pain
- DMS induces astrocyte reactivity and inflammatory cytokine release
- Blockade of DMS production with inhibitors may provide pain relief for Chiari patients without side effects.

References

1. Patti, G. J, Yanes, O., Shriver, L.P., et al. Metabolomics implicates altered sphingolipids in chronic pain of neuropathic origin. Nature chemical biology 8, 232-234, (2012).