Role of the spinal TrkB-NMDA receptor link in the BDNF-induced long-lasting mechanical hyperalgesia in the rat: A behavioural study

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EUROPEAN JOURNAL OF PAIN
Volume: 21
Issue: 10
Pages: 1688-1696
DOI: 10.1002/ejp.1075
Published: NOV 2017
Document Type: Article

View Journal Impact

Abstract

BackgroundIntrathecal/intracisternal BDNF in rodents produces long-lasting hyperalgesia/allodynia, which implies BDNF plays a role in the establishment and maintenance of central sensitization. Both self-regeneration of endogenous BDNF and neuroplastic modifications of spinal NMDA receptors downstream TrkB signalling could be involved in such enduring hyperalgesia. We investigated to what extent BDNF by itself could participate in the generation and maintenance of mechanical hyperalgesia using pharmacological tools.

MethodsWe studied sensitivity of mechanical hyperalgesia induced by a single intrathecal (i.t.) injection of BDNF (3ng/10L i.t.) administered at time zero, for: (1) chronic NMDA receptor inhibition with subcutaneously implanted 7-day delivery osmotic pumps loaded with ketamine; (2) TrkB receptor inhibition with intraperitoneal (i.p.) cyclotraxine-B; and (3) chronic glial inhibition with repeated propentofylline i.t. injections. Nociceptive threshold to paw pressure, tested on days -3, 0, 3, 7, 10 and 14, was used as the index of central sensitization. Locomotor patterns and food and water consumption were assessed with LABORAS.

ResultsChronic ketamine prevented the mechanical hyperalgesia induced by BDNF, without affecting locomotion and food and water consumption. After pump depletion, a late hyperalgesic response to paw pressure stimulation emerged, which can be lastingly antagonized by cyclotraxine-B. Chronic propentofylline treatment irreversibly suppressed BDNF-induced hyperalgesia.

ConclusionActivation of NMDA receptors downstream to TrkB signalling is essential for

behavioural expression of the mechanical hyperalgesia induced by intrathecal BDNF. However, maintenance of the hyperalgesia depends mainly from self-regenerating glial BDNF rather than from a NMDA receptor-dependent form of neuroplasticity.

SignificanceIntrathecal BDNF induces long-lasting central sensitization via a glial-likely BDNF self-regenerating mechanism, whose behavioural expression depends on downstream activation of NMDA receptors. This knowledge suggests that TrkB antagonists could represent an interesting lead for the development of novel therapeutic strategies for some chronic pain conditions.

Keywords

KeyWords Plus:DORSAL-ROOT GANGLION; NEUROTROPHIC FACTOR; NEUROPATHIC PAIN; NERVE LIGATION; TERM POTENTIATION; SCIATIC-NERVE; MICROGLIA CAUSES; ACTIVATION; HORN; CORD

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Funding

Funding Agency	Grant Number
Centro para el Desarrollo de la Nanociencia y la Nanotecnologia (CEDENNA)	FB0807

Direccion de Investigacion Cientifica y Tecnologica (DICYT) of the University of Santiago of Chile	021543CC
Proyectos Basal USA Universidad de Santiago de Chile	1555 - Vridei 021743CC_PUBLIC

View funding text

Publisher

WILEY, 111 RIVER ST, HOBOKEN 07030-5774, NJ USA

Journal Information

- **Impact Factor:** Journal Citation Reports

Categories / Classification

Research Areas: Anesthesiology; Neurosciences & Neurology

Web of Science Categories: Anesthesiology; Clinical Neurology; Neurosciences

Document Information

Language: English

Accession Number: WOS:000412603400007

PubMed ID: 28670835

ISSN: 1090-3801

eISSN: 1532-2149