American Pain Society
RESEARCH
EDUCATION
TREATMENT
ADVOCACY
PUBLISHED BY ELSEVIER

The Journal of Pain, Vol 14, No 10 (October), 2013: pp 1173-1184
*Available online at www.jpain.org and www.sciencedirect.com*

# Maternal Deprivation Is Associated With Sex-Dependent Alterations in Nociceptive Behavior and Neuroinflammatory Mediators in the Rat Following Peripheral Nerve Injury

Nikita N. Burke,* Ricardo Llorente,† Eva M. Marco,† Kezanne Tong,* David P. Finn,‡ Maria-Paz Viveros,† and Michelle Roche*

**Physiology and ‡Pharmacology and Therapeutics, School of Medicine, NCBES Centre for Pain Research and Galway Neuroscience Centre, National University of Ireland, Galway, Ireland.*
*†Departamento de Fisiología (Fisiología Animal II), Facultad de Ciencias Biológicas, Universidad Complutense de Madrid & Instituto de Investigación Sanitaria del Hospital Clínico San Carlos (IdISSC), Madrid, Spain.*

**Abstract:** **Early-life stress is associated with an increased risk of developing affective disorders and chronic pain conditions. This study examined the effect of maternal deprivation (MD) on nociceptive responding prior to and following peripheral nerve injury (L5-L6 spinal nerve ligation [SNL]). Because neuroimmune signaling plays an important role in pain and affective disorders, associated alterations in glial and cytokine expression were assessed in key brain regions associated with emotional and nociceptive responding, the hippocampus and prefrontal cortex. MD female, but not male, rats exhibited thermal hypoalgesia and mechanical allodynia compared with control (non-MD) counterparts. SNL resulted in mechanical and cold allodynia in MD and control rats of both sexes. However, MD females exhibited enhanced SNL-induced allodynic responding compared with non-MD counterparts. Interleukin 6 (IL-6) expression was reduced in the prefrontal cortex of MD-SNL males when compared with non-SNL counterparts. Glial fibrillary acidic protein and IL-1β expression in the hippocampus of MD-SNL males was increased compared with non-MD controls. MD-SNL females exhibited reduced tumor necrosis factor alpha in the prefrontal cortex with a concomitant increase in IL-6 and tumor necrosis factor alpha expression in the hippocampus, compared with either MD or SNL alone. In conclusion, MD female, but not male, rats exhibit enhanced nociceptive responding following peripheral nerve injury, effects that may relate to the distinct neuroinflammatory profile observed in female versus male rats.**

***Perspective:*** ***This study demonstrates that females rats exposed to early-life stress exhibit enhanced neuropathic pain responding, effects that are associated with alterations in neuroinflammatory mediators. Increased understanding of the interactions among early-life stress, gender, and pain may lead to the identification of novel therapeutic targets for the treatment of chronic pain disorders.***

© 2013 by the American Pain Society

***Key words:*** *Maternal deprivation, spinal nerve ligation, mechanical allodynia, cold allodynia, cytokines.*

Received March 9, 2013; Revised April 24, 2013; Accepted May 2, 2013.
The authors would like to gratefully acknowledge funding received from the discipline of Physiology and the Millennium Fund, National University of Ireland Galway; the International Brain Research Organisation who provided a Project InEurope short-stay travel grant to N.N.B; and Instituto de Salud Carlos III, Redes temáticas de Investigación Cooperativa en salud: Red de trastornos adictivos RD2012/0028/0021. N.N.B. is a recipient of College of Medicine, Nursing and Health Sciences, National University of Ireland Galway, Doctoral Fellowship.
The authors declare no conflict of interest.
Supplementary data accompanying this article are available online at www.jpain.org and www.sciencedirect.com.
Address reprint requests to Michelle Roche, PhD, Physiology, School of Medicine, National University of Ireland, Galway, University Road, Galway, Ireland. E-mail: Michelle.roche@nuigalway.ie
1526-5900/$36.00
© 2013 by the American Pain Society
http://dx.doi.org/10.1016/j.jpain.2013.05.003

Adverse early-life events are associated with a predisposition to developing psychiatric disorders[1,21,44] and chronic pain conditions[10,16,36] in later life. Manipulation of mother-pup interactions has been used extensively as a model of early-life stress in rodents to study underlying neurobiological mechanisms.[7] One of the most widely used methods involves the separation of the mother from her pups during the first 2 weeks of life, a critical period in the development of nociceptive, sensory, emotional, and social functions.[4,15,18,37] In rodents, 2 experimental procedures are primarily used: a prolonged single period (24 hours) of maternal deprivation (MD)[15,51] and episodic brief periods (3–6 hours) of maternal separation.[29] A single

episode of MD on postnatal day (PND) 9 results in behavioral changes in adolescence and adulthood that resemble those found in the affective disorders, including depressive-like responses,[31] enhanced impulsivity,[38] disruption in pre-pulse inhibition,[14,15] and cognitive deficits.[33,39] Despite the robust changes in affective behavior, few studies have investigated the effect of early-life stress on nociceptive responding. Episodic maternal separation has been shown to result in enhanced affective pain behavior,[50] visceral hypersensitivity,[6,8,19,40] and inflammatory hyperalgesia.[50] However, the effect of a single period of MD on nociceptive responding has not been examined, nor have there been studies investigating the effect of early-life stress on neuropathic pain responding. The present study sought to address these 2 gaps in knowledge.

Neuroinflammatory processes are now well recognized to play important roles in the pathophysiology of stress-related psychiatric disorders and chronic pain.[3,9] We therefore hypothesized that MD-related alterations in sensory and affective responding would be accompanied by altered expression of neuroinflammatory molecules in discrete brain regions involved in pain and affect. Stressful rearing conditions are associated with a number of neuroimmune alterations such as downregulated expression of microglial markers, cytokines (interleukin [IL]-10, IL-1β), chemokines (CCL7), and receptors (IL-5 receptor-alpha, CCR4) in the brain.[13] In addition, early-life stress reportedly reduces the expression of astrocytic markers (S100β, glial fibrillary acidic protein [GFAP]) in the anterior cingulate and precentral medial cortices[42] and increases astrocyte density in the hippocampus and cerebellum.[32,34,39] However, it is unknown if alterations in proinflammatory cytokines occur in key brain regions involved in emotional and nociceptive processing in the MD model. It is well established that neuropathic pain induces alterations in inflammatory processes at the level of the spinal cord.[23,47] However, a number of recent studies have indicated that peripheral nerve injury is also associated with increased supraspinal neuroinflammatory processes. Specifically, chronic constriction injury is associated with increased hippocampal tumor necrosis factor alpha (TNF-α) levels[22] whereas spared nerve injury is associated with increased IL-1β expression in the frontal cortex and GFAP expression in the periaqueductal gray.[2,11,45] Chronic stress prior to peripheral nerve injury has been shown to exacerbate mechanical allodynia and depressive behavior and augment injury-induced IL-1β expression in the frontal cortex,[45] thus indicating possible functional interactions among stress, neuroinflammation, and pain. Thus, we hypothesized that early-life stress–induced changes in affective and nociceptive behavior may be accompanied by alterations in supraspinal neuroinflammatory processing.

The aims of the current study were to examine the effect of MD on nociceptive and neuropathic pain behavior in adulthood. Glial activation and cytokine expression were assessed in the prefrontal cortex (PFC) and hippocampus, key brain regions involved in emotional and nociceptive processing,[12,35] in order to determine if MD-induced alterations in behavioral responding are associated with concomitant alterations at the neuroimmune level. As sexually dimorphic effects on behavior and neuroendocrine function occur following MD,[39,51,52] responses were evaluated in both male and female animals.

## Methods

### Animal Husbandry

Experimental subjects were the offspring of albino Wistar male and female rats purchased from Harlan Interfauna Ibérica SA (Barcelona, Spain) mated (1 male × 2 females) in the animal facility approximately 2 weeks after their arrival. Animals were housed in standard facilities on a reverse light-dark cycle (lights on at 2000 hours). On the day of birth [PND 0], litters were sex-balanced, weighed, and culled to 8 pups per dam (4 males and 4 females). Testing began in adulthood, animals older than PND 69, and all testing was carried out during the dark phase. The experimental protocol was carried out in accordance with the guidelines and approval of the Animal Care and Research Ethics Committee, National University of Ireland, Galway, under license from the Irish Department of Health and Children and in compliance with the European Communities Council directive 86/609.

### MD

The MD protocol took place on PND 9 as previously described.[31,32] In brief, on PND 9, half of the litters were submitted to 24 hours of MD, that is, dams removed from their home cages at 0900 hours and pups left undisturbed in their corresponding home cage (in the same room), until PND 10, when dams were returned to their corresponding home cages. Based on results from our laboratory and others,[30,51,52,56] we believe the MD model depends on sensorimotor, nutritional, and temperature insults to the neonate, the combination of which synergize to establish the long-term changes in the model. At weaning (PND 22), animals were housed in pairs of sibling animals of the same sex. Body weight was recorded from control (Co) and MD pups at PNDs and PND 10, and thereafter every 6 days from PND 22 to 64.

### Experimental Design

The experimental design is presented in Fig 1, with testing beginning in adulthood. Essentially, animals were tested in the holeboard test, elevated plus maze, and open field test to assess exploration, anxiety-like behavior, and locomotor activity, respectively, whereas nociceptive responding was assessed using the hot plate test (noxious thermal stimulus), von Frey test (mechanical stimulus), and the acetone-drop test (cold stimulus). Animals were then allocated to 1 of 4 groups: control non–spinal nerve ligation (Co-NSNL) (male n = 8, female n = 10), control spinal nerve ligation (Co-SNL) (male n = 10, female n = 10), MD-NSNL (male n = 10,

Download English Version:

https://daneshyari.com/en/article/5880820

Download Persian Version:

https://daneshyari.com/article/5880820

Daneshyari.com