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Research Report

Characterization of nociceptive responses to bee venom-induced inflammation in neonatal rats

Mengmeng Li[a,c], *Huisheng Chen*[b], *Jiaguang Tang*[a], *Jianhua Hao*[a], *Jun Chen*[b,*], *Jianren Mao*[c,**]

[a]*Department of Anaesthesiology, The First Affiliated Hospital of Chinese PLA General Hospital, Beijing, China.*
[b]*Institute for Biomedical Sciences of Pain, Tangdu Hospital, Fourth Military Medical University, 1 Xinsi Road, Baqiao District, Xi'an, Shaanxi 710038, China*
[c]*MGH Center for Translational Pain Research, Department of Anaesthesia, Critical Care and Pain Medicine, Massachusetts General Hospital, Harvard Medical School, 15 Parkman Street, Boston, MA 02114, USA*

ARTICLE INFO

Article history:
Accepted 4 July 2012
Available online 16 July 2012

Keywords:
Development
Bee venom
Inflammatory pain
Postnatal day
Persistent spontaneous nociception
Hyperalgesia

ABSTRACT

To assess developmental characteristics of nociceptive responses induced by bee venom (BV) injection in neonatal rats, we exposed pups to intra-plantar injection of various BV concentrations given at different time points between postnatal day 1 and day 28 (P1–P28). Persistent spontaneous nociception (PSN) as well as thermal and mechanical nociceptive response was compared before and after a BV injection. There were distinct age-related changes in the baseline paw withdrawal thermal latency (PWTL) and paw withdrawal mechanical threshold (PWMT) when examined on P1, P4, P7, P14, P21, and P28. The lowest and highest baseline PWTL was shown on P1 and P7, respectively, and PWTL was unchanged from P7 to P28. In contrast, the baseline PWMT remained low before P21 but increased dramatically afterward. Neonatal rats receiving intra-plantar BV injection showed a time-dependent change in nociceptive responses, including (1) a dose-related increase in PSN from P1 to P28; (2) a non-specific decrease (indistinguishable between saline and BV injection) in PWTL and PWMT up to P14 and P21, respectively; and (3) a specific decrease (in response to BV injection only) in PWTL and PWMT after P14 and P21, respectively. These findings indicate that characteristic changes in the baseline and BV-induced nociceptive response are both time-dependent and modality-specific in neonatal rats. The data reveal a critical postnatal period during which nociceptive stimulation could have a significant influence on nociceptive behavior in adult rats and suggest that preclinical models of neonatal nociception should be evaluated according to different postnatal time points.

Abbreviations: mEPSC, the miniature excitatory postsynaptic current; EPSCs, excitatory postsynaptic currents; IPSCs, Inhibitory postsynaptic currents; α2-AR, α2-adrenergic receptor; PAG, the midbrain periaqueductal grey; RVM, retroventral medulla

*Corresponding author. Fax: +1 86 29 84777945.
**Corresponding author. Fax: +1 617 726 8807.
E-mail addresses: junchen@fmmu.edu.cn (J. Chen), jmao@partners.org (J. Mao).

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http://dx.doi.org/10.1016/j.brainres.2012.07.005

1. Introduction

Recent animal studies have shown that anesthetic agents could induce neuronal apoptosis and subsequent abnormal behaviors in immature animals under certain conditions (Istaphanous and Loepke, 2009; Lopeke and Soriano, 2008). In addition, a large body of evidence indicates that inflammation and/or nociception at the postnatal stage may influence the development and maturity of nociceptive circuits due to long-term changes in the somatosensory and pain processing (Al-Chaer et al., 2000; Hohmann et al., 2005; Laprairie et al., 2008; Lidow et al., 2001; Ruda et al., 2000; Wang et al., 2004). Therefore, the necessity of providing adequate anesthesia in infants and young children may have both beneficial and adverse impacts in the clinical setting (McGowan and Davis, 2008; Sanders et al., 2008).

Human studies have demonstrated a possible relationship between neonatal injury and changes in pain response (Andrews and Fitzgerald, 1994; Craig et al., 1993; Gibbins et al., 2008; Johnston et al., 1993). Specifically, it has been reported that repeated heel lance in neonatal exacerbates the response to heel injury (Anand, 1998; Fitzgerald et al., 1989; Simons et al., 2003), whereas invasive, albeit minor, procedures in premature infants decreases nociceptive behavior (Johnston and Stevens, 1996). However, the difference between these reports may be related to the timeframe of observation. For example, Fitzgerald et al. (1989) examined reflex responses within 72 h, indicating peripheral and spinal cord sensitivity, whereas Johnston and Stevens (1996) reported facial action differences following pain exposure over four weeks. In preclinical studies, a number of animal models have been used to study neonatal inflammation and nociceptive behavior, including models using formalin, carrageenan, capsaicin, complete Freund's adjuvant (CFA), or bee venom (BV). Formalin injection produces nociception lasting about 30 min in young animals but an hour in adults (Abbott et al., 1995; Guy and Abbott, 1992). While formalin produces a biphasic response in rats older than 25 day, it produces only the first phase (acute) response in rats younger than 15 day (Teng and Abbott, 1998). Moreover, previous behavioral and electrophysiological studies have shown that thermal or mechanical hyperalgesia was not produced in postnatal rats by subcutaneous formalin (Chen et al., 2003a, 2003b; Chen and Chen, 2001; You and Arendt-Nielsen, 2005). In contrast, carrageenan elicited nociceptive behavior was detectable up to 2 weeks following a single injection (Alvares et al., 2000), whereas injection of CFA resulted in long-term activation of immune responses and nociceptive behavior (Billiau and Matthys, 2001).

Despite these previous reports, the impact of noxious stimulation given at various neonatal stages on nociceptive response remains unclear. It has been suggested that animal models of nociception should include several important features including minimum inter-individual and inter-model differences as well as integration of both acute and persistent nociceptive responses (Chen, 2008). In this regard, BV-induced nociception has been shown in adult rats to be a useful model as it consists of an immediate spontaneous nociceptive response, which lasts for more than 1 h, and a persistent phase of thermal or mechanical hypersensitivity for up to four days (Chen et al., 1999, 2003a, 2003b; Kumamoto, 2007; Lariviere and Melzack, 2000).

In the present study, we used intra-plantar BV injection as a model of inflammatory nociception to examine the developmental characteristics of nociceptive responses in neonatal rats. Intra-plantar injection of various BV concentrations was given to pups between postnatal day 1 and day 28 (P1, P4, P7, P14, P21, P28). Persistent spontaneous nociception (PSN) as well as paw withdrawal thermal latency (PWTL) and paw withdrawal mechanical threshold (PWMT) was compared before and after each BV injection.

2. Results

2.1. *Postnatal changes in the baseline PWTL and PWMT*

Neonatal pups showed distinct age-related differences in the baseline nociceptive response when examined on P1, P4, P7, P14, P21, and P28 (Fig. 1). Neonatal pups had the lowest and highest baseline PWTL on P1 and P7, respectively, and then remained stable from P7 to P28 (Fig. 1A). In contrast, the baseline PWMT remained very low between P1 and 21 and then dramatically increased on P28. The baseline PWMT on P28 was 10-fold higher than that before P21 (Fig. 1B).

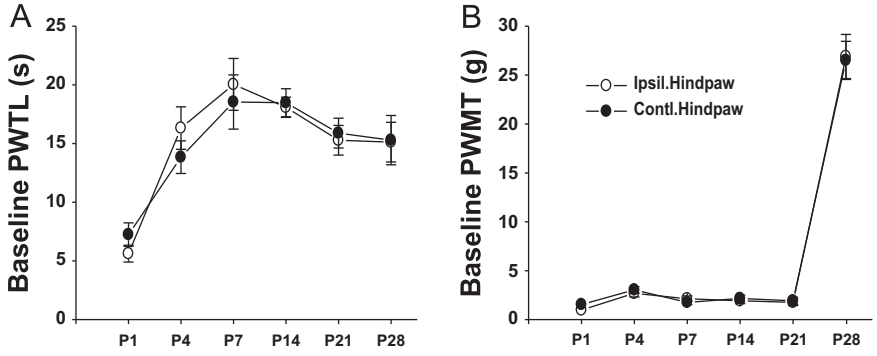

Fig. 1 – *Baseline paw withdrawal thermal latency* (PWTL) *and paw withdrawal mechanical threshold* (PWMT) *in neonatal rats* A: Neonatal rats showed the lowest and highest baseline PWTL at P1 and P7, respectively. B: Baseline PWMT remained very low between P1 and 21 but was increased at P28. (n=32–40). Ipsil. Hindpaw: Ipsilateral hindpaw; Contl. Hindpaw: contralateral hindpaw. Error bars indicate SEM.