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Review article

Persistent changes in peripheral and spinal nociceptive processing after early tissue injury☆

Suellen M. Walker [a,b], Simon Beggs [c], Mark L. Baccei [d,*]

[a] Pain Research (Respiratory Critical Care and Anaesthesia), UCL Institute of Child Health, Department of Anaesthesia and Pain Medicine, Great Ormond Street Hospital for Children NHS Foundation Trust, London, United Kingdom
[b] Department of Neuroscience, Physiology and Pharmacology, University College London, London, United Kingdom
[c] Program in Neurosciences and Mental Health, The Hospital for Sick Children and Faculty of Dentistry, University of Toronto, Toronto, Ontario, Canada
[d] Pain Research Center, Dept. of Anesthesiology, University of Cincinnati, Cincinnati, OH USA

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ABSTRACT

It has become clear that tissue damage during a critical period of early life can result in long-term changes in pain sensitivity, but the underlying mechanisms remain to be fully elucidated. Here we review the clinical and preclinical evidence for persistent alterations in nociceptive processing following neonatal tissue injury, which collectively point to the existence of both a widespread hypoalgesia at baseline as well as an exacerbated degree of hyperalgesia following a subsequent insult to the same somatotopic region. We also highlight recent work investigating the effects of early trauma on the organization and function of ascending pain pathways at a cellular and molecular level. These effects of neonatal injury include altered ion channel expression in both primary afferent and spinal cord neurons, shifts in the balance between synaptic excitation and inhibition within the superficial dorsal horn (SDH) network, and a 'priming' of microglial responses in the adult SDH. A better understanding of how early tissue damage influences the maturation of nociceptive circuits could yield new insight into strategies to minimize the long-term consequences of essential, but invasive, medical procedures on the developing somatosensory system.

Contents

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* Corresponding author at: Pain Research Center, Dept. of Anesthesiology, University of Cincinnati Medical Center, 231 Albert Sabin Way, Cincinnati, OH 45267, USA.
E-mail address: mark.baccei@uc.edu (M.L. Baccei).

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1. Impact of early life injury: clinical studies

Neonates and infants who require major surgery or management in a neonatal intensive care unit (NICU) are exposed to significant painful stimuli at a time when the developing nervous system is sensitive to changes in sensory experience (Fitzgerald and Walker, 2009). Evidence for associations between early life pain and adverse neurodevelopmental outcomes, persistent changes in sensory processing, and altered responses to future pain is increasing. However, differences in study methodology, included populations, and outcome measures mean that reported effects of early life pain vary in degree, direction (increase or decrease in pain sensitivity), and functional impact. Sources of variability (Walker, 2013) can include:

i) the type and intensity of initial pain and injury. This may encompass variable numbers and types of procedures or surgery in otherwise healthy neonates or infants, through to repeated interventions in preterm-born neonates with multiple comorbidities.
ii) developmental stage at the time of the initial insult can range from neonates born extremely preterm (i.e. before 26 weeks gestation) through to infancy.
iii) age at subsequent assessment. At older ages more detailed outcomes can be assessed, but the increased time interval may also increase the potential for other family, social, environmental or health-related factors to influence reported associations between early life experience and current pain.
iv) the outcome measured, and particularly the intensity of subsequent test stimuli. Examples include: observer ratings and evaluation of behavioral responses to future clinical procedures (e.g. observer pain score and duration of cry following immunization); psychophysical measures of sensory detection/pain thresholds at baseline or in response to noxious experimental stimuli (e.g. prolonged heat stimulus, cold pressor test, pressure algometry); or cortical EEG or fMRI responses to noxious stimuli.

These factors and related studies are discussed in recent reviews (Walker, 2013; Ranger and Grunau, 2014; Vinall and Grunau, 2014). Here, the focus is on clinical studies evaluating changes in sensory processing and spinal reflex thresholds, and their parallels with laboratory studies investigating the pattern, mechanisms and age-related susceptibility to long-term effects following neonatal injury.

1.1. Acute injury-related changes in sensory threshold

Noxious stimuli produce acute physiological and behavioral responses even in preterm neonates, and increases activity in spinal and cortical nociceptive circuits (Fitzgerald and Walker, 2009; Slater et al., 2010; Walker, 2013). Although less well-tuned than at older ages, spinal reflex thresholds encode stimulus intensity in neonates and infants (Andrews and Fitzgerald, 1994; Slater et al., 2010) and intense or repeated stimuli lead to sensitization. Following repeated heel lance blood sampling, the hindlimb mechanical withdrawal threshold is reduced, but sensitivity is reversed by topical local anesthesia (Fitzgerald et al., 1988). By contrast, sucrose does not alter acute hindlimb reflex responses to heel lance (Slater et al., 2010) or prevent enhanced behavioral responses following repeated blood sampling (Taddio et al., 2009). Reductions in abdominal skin reflex thresholds quantify sensitization around surgical wounds in infants, with partial reversal by bolus doses of opioids (Andrews et al., 2002). In infants with unilateral hydronephrosis, referred visceral hyperalgesia was quantified by reductions in the threshold of the ipsilateral abdominal skin reflex (Andrews et al., 2002).

1.2. Persistent changes in sensory threshold following neonatal injury

Although peripheral tissue injury acutely reduces sensory thresholds, a more complex pattern of sensory changes is seen at older ages, with effects dependent on the intensity of the stimulus. Quantitative Sensory Testing (QST) has identified persistent changes in sensory processing following neonatal intensive care and/or surgery. Mechanical light touch detection thresholds around neonatal thoracotomy wounds were reduced 10–12 years following surgery (Schmelzle-Lubiecki et al., 2007), with a trend to greater change than around smaller scars related to chest drain insertions (Walker et al., 2009a). Baseline sensitivity to thermal stimuli was also reduced at different body sites (thenar eminence, face, or chest) in 9–12 year old children following NICU (Hermann et al., 2006; Walker et al., 2009a). The degree of change compared to healthy term-born controls was more marked in those born preterm (Hermann et al., 2006) and those who also required surgery (Walker et al., 2009a) suggesting that both the degree of injury and age at the time of initial injury may be contributing factors.

Although baseline thermal thresholds were higher (i.e. reduced sensitivity), a prolonged heat stimulus at pain threshold (Hermann et al., 2006) or repeated trials (Hohmeister et al., 2010) unmasked enhanced perceptual sensitization in preterm born children who had required NICU management. This dual pattern of generalized baseline *hypo*algesia, but *hyper*algesia in response to a more intense noxious stimulus, has also been identified in laboratory studies (see subsequent section). Sensitivity to a noxious mechanical stimulus (reduced pressure pain threshold) and an increased number of tender points was reported in adolescents 12–18 years following NICU (Buskila et al., 2003). The number of studies utilizing QST and experimental pain tasks in control and clinical populations of children is increasing, although there is some variation in methodology and in reported effects of age and sex (Myers et al., 2006; Blankenburg et al., 2011; Birnie et al., 2012; de Graaf et al., 2012; Birnie et al., 2014). Ongoing follow-up and sensory testing of NICU cohorts at older ages, when more complex psychophysical tests can be performed, will further clarify the pattern or persistence of sensory change.

2. Impact of early life injury: Laboratory studies

Despite increasing clinical evidence for associations between early life experience and altered sensory processing or nociceptive sensitivity, attributing causation is more problematic, and there have been limited studies evaluating the effect of the same insult at different ages. Preclinical studies can control for potential confounding factors and provide essential information that cannot be achieved with clinical studies alone, by:

i) comparing the impact of the same injury across a range of postnatal ages to establish a critical period for altered response;
ii) identifying underlying age- and injury-dependent mechanisms; and
iii) evaluating prevention or modulation by analgesia to inform subsequent clinical research and practice.

A range of injury models have been used to investigate long-term effects of early life pain and injury (Walker, 2013; Schwaller and Fitzgerald, 2014). Hindpaw inflammation is a well-established model,