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Review Article

Nerve injury and neuropathic pain — A question of age

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ABSTRACT

The effects of peripheral nerve injury on somatosensory processing and pain are highly dependent upon the age at which the damage occurs. Adult nerve injury rapidly triggers neuropathic pain, but this is not so if the same nerve injury is performed in animals below postnatal day (P) 28, consistent with observations in paediatric patients. However, longitudinal studies show that pain hypersensitivity emerges later in life, when the animal reaches adolescence, an observation that could be of clinical importance. Here we discuss the evidence that the central consequences of nerve damage are critically determined by the status of neuroimmune regulation at different ages. In the first postnatal weeks, when spinal somatosensory circuits are undergoing synaptic reorganisation, the 'default' neuroimmune response is skewed in an anti-inflammatory direction, suppressing the excitation of dorsal horn neurons and preventing the onset of neuropathic pain. As animals grow up and the central nervous system matures, the neuroimmune profile shifts in a pro-inflammatory direction, unmasking a 'latent' pain response to an earlier nerve injury. The data predicts that nerve injury in infancy and childhood could go unnoticed at the time, but emerge as clinically 'unexplained' or 'functional' pain in adolescence.

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1. Introduction — The ontogeny of neuropathic pain

1.1. The first phase — No neuropathic pain

Peripheral nerve damage in early life does not simply remove a source of sensory input from the somatosensory system, it triggers great change in neural circuitry and leads to long term alterations spinal somatosensory function. However, the nature of these changes is dependent upon when exactly, in terms of postnatal age, this nerve damage occurs.

A major consequence of nerve damage, in adult man and laboratory animals, is the onset of neuropathic pain, characterised by allodynia and pain hypersensitivity from the partially denervated regions (Gilron et al., 2015). Thus, spared nerve injury (SNI), a classic partial denervation model (Decosterd and Woolf, 2000), produces robust mechanical allodynia, measured as a fall in hindpaw cutaneous sensory threshold to 16% of controls, within one postoperative day and lasting at least 28 days (Howard et al., 2005).

Strikingly, neuropathic pain does not arise if exactly the same nerve injury is performed in young animals. Rat pups aged 3, 10 and 21 days at the time of surgery do not display equivalent allodynia at any time up to 28 days later (Howard et al., 2005). Only at postnatal day (P) 33 does SNI lead to a significant and persistent allodynia with the threshold falling to 55% of control values. A comparable lack of neuropathic pain behaviour is observed in other models of juvenile nerve injury: chronic constriction injury (CCI) causes a clear allodynia in adult rats but no change in hindpaw sensitivity when performed at 10 days of age (Howard et al., 2005) and the more proximal injury, spinal nerve ligation, causes only transient allodynia when performed at P14 (Ririe and Eisenach, 2006). This data has been confirmed in other studies (Costigan et al., 2009; Moss et al., 2007; Vega-Avelaira et al., 2009) and recently extended beyond mechanical allodynia to cool and cold allodynia, and altered weight bearing, all of which develop within a few days of adult SNI but are absent following SNI performed at P10 (McKelvey et al., 2015).

This finding is consistent with clinical experience. Neuropathic pain following nerve injury is rare in infants, and only very few reports exist before 5–6 years of age (Anand and Birch, 2002; Howard et al., 2014; Walco et al., 2010) and the incidence of neuropathic pain increases with age at which nerve damage occurs (Atherton et al., 2008). Thirteen years is the median age of onset for paediatric neuropathic pain syndromes, such as phantom pain, complex regional pain syndrome, and peripheral neuropathy pain (Walco et al., 2010) but the reasons for this are not known. Although many of the underlying disease states involving neuropathic pain are less frequent in children, it is also evident that nerve damage is more likely to trigger pain in late childhood and adolescence than at younger ages.

1.2. The delayed phase — Late onset neuropathic pain

Infants of all mammalian species tested are capable of displaying robust nociceptive responses to noxious mechanical, thermal and chemical stimulation and develop persistent allodynia and hyperalgesia in response to inflammation of the skin, joints and viscera. So the question remains as to why there is a specific absence of neuropathic pain following nerve injury at younger ages. Clues to this may provide a new insight into this most unpleasant of pain conditions.

Recent longitudinal studies have discovered a novel consequence of juvenile nerve injury. Mechanical hypersensitivity, characteristic of neuropathic pain, does occur but only later in life. While spared nerve injury (SNI) at (P10) has no effect on sensory thresholds in the first 2–3 weeks post-P10 surgery, after that time period, beginning at 21 days post-surgery (P31), the SNI group develop significant hypersensitivity (Vega-Avelaira et al., 2012). This delayed adolescent onset hypersensitivity is also observed using cold stimulation and weight bearing tests but not noxious heat stimulation (McKelvey et al., 2015).

Interestingly, clinical investigation of phantom limb pain in adolescence shows that children with the earliest amputations do develop phantom pain but only after a considerable delay, of a mean of 7 years (Melzack et al., 1997). Furthermore several complex pain syndromes (e.g. CRPS) that emerge in older children are associated with little or no measurable disease activity or inflammation at the time of presentation and are clinically defined as 'functional' or 'medically unexplained' (Bromberg et al., 2014). This led us to hypothesise that the changes in pain processing over infancy, childhood and adolescence may be of special significance in understanding the maturation of neuropathic pain.

In this review we examine the immediate and longer term changes in dorsal horn nociceptive circuits that follow experimental nerve injury in infant, juvenile and adolescent rats. We present evidence that the clue to the late development of neuropathic pain lies in the maturation of neuroimmune regulation of pain pathways in the spinal cord dorsal horn.

2. Cellular effects of nerve injury in early life: The first phase (no pain)

2.1. Cell death and compensatory sprouting

In adults, there is some evidence for cell death in the dorsal root ganglia and dorsal horn following nerve injury but this is limited and only observed after a considerable time post-injury (Scholz et al., 2005; Tandrup et al., 2000). The situation is quite different following nerve injury in the immediate postnatal period. Sensory neurons in the rat dorsal root ganglion (DRG) are still undergoing axonal growth and naturally occurring cell death in the first postnatal week and are highly dependent upon their peripheral target skin and muscle for survival (Chong et al., 1992; Coggeshall et al., 1994). As a result, nerve damage in the immediate postnatal period causes substantial and rapid cell death (of up to 75% neurons) in the dorsal root ganglion (Himes and Tessler, 1989; Whiteside et al., 1998; Yip et al., 1984).

The loss of sensory neurons following early nerve damage triggers axonal sprouting within the damaged nerve itself and collateral sprouting of adjacent intact afferent terminals into the denervated region of the dorsal horn. For example, following sciatic nerve section at postnatal day (P) 1, the adjacent saphenous nerve dorsal horn terminal field doubles in size, expanding into areas normally occupied by sciatic nerve terminals, with single afferents growing up to 2000 μm into the deafferented sciatic terminal field (Fitzgerald, 1985; Fitzgerald et al., 1990; Fitzgerald and Vrbová, 1985). Both A fibres and substance P- and CGRP-expressing C fibres are involved in this sprouting (Reynolds and Fitzgerald, 1992; Shortland and Fitzgerald, 1994). The A fibre terminals of surviving axotomized primary afferent neurons also sprout dorsally into lamina II and join the invading intact A and C fibres contributing to the overlap in central representation of nerve territories (Shortland and Fitzgerald, 1994).

Importantly, the new sprouted terminals form functional connections with dorsal horn neurons, such that cells that normally only respond to inputs from the damaged nerves now respond to intact inputs from adjacent body areas. For example, after neonatal sciatic nerve section, dorsal horn neurons with receptive fields in the saphenous skin region can be found throughout L3, L4 and L5 segments, while they are normally restricted to L3 and rostral L4 (Shortland and Fitzgerald, 1991) and stimulation of nearby intact nerves evoke greater fos activation in denervated areas of the dorsal horn (Shortland and Molander, 2000). Nevertheless, loss of primary afferent input apparently withdraws trans-synaptic trophic support from the dorsal horn and projection neurons have substantially fewer primary dendrites and secondary branches compared to controls following neonatal nerve damage (Fitzgerald and Shortland, 1988) accompanied by a small loss of interneurons (Lowrie and Lawson, 2000).

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