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REVIEW

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A review of perinatal acute pain: treating perinatal pain to reduce adult chronic pain

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Abstract Changes in neural connections and activity after an acute insult are hypothesised to contribute to chronic pain syndromes in mature experimental animals and humans. Over the last decade, studies have suggested that exposure to repeated painful procedures during the early perinatal period results in profound changes in sensitivity of nociceptive pathways. Both animal and human studies show that early pain experiences increase pain responses beyond the period of infancy. These data suggest a need to increase implementation of guidelines for minimising pain exposures during infancy. In addition, an experimental perinatal pain model may provide a unique opportunity to study the effects on the nervous system of both painful insults and pre-emptive analgesia.

Keywords Circumcision · Migraine · Neural plasticity · Perinatal pain · Pre-emptive analgesia

Introduction

Remodelling of nociceptive pathways after exposure to a noxious insult is hypothesised to contribute to the development of chronic pain that persists long after the insult has been removed and healing has occurred [1, 2]. Experimental models for both arthritic and neuropathic pain support the importance of neural plasticity for persistent pain complaints [3, 4]. These data suggest that initial pain exposure sets the stage for subsequent increased pain sensitivity, which may be experienced as increased risk to a variety of chronic pain conditions.

Until recently, newborns and children were considered to be relatively insensate to painful stimuli. Furthermore, a belief that babies would not remember their painful experience reduced efforts to minimise painful procedures and use pre-emptive analgesia before procedures. Over the last decade, studies have shown that children, including newborns, do perceive noxious stimuli as painful. By measuring heart rate, oxygen saturation, mean arterial pressure and behavioural response, Porter et al. [5] showed that newborns respond to painful stimuli, similar to adults. In addition, even very premature infants were shown to negatively respond to pain and to be able to differentiate stimulus intensity, with a stronger response shown for more invasive procedures.

Medical staff are also more aware that paediatric procedures are often perceived as painful. A survey of doctors and nurses working in intermediate or intensive care

nurseries showed that 90% believed infants felt the same or more pain from common procedures than adults [6]. Tracheal suctioning, gavage tube insertion and umbilical catheter insertion were considered only mildly painful. Moderately painful procedures included intubation, arterial or venous cutdown, lumbar puncture, intramuscular injection, intravenous or intra-arterial line placement, and heel stick. Circumcision and chest tube insertion were considered to cause severe pain. Despite the awareness that these procedures resulted in a pain response from newborns, analgesic measures were not considered to be routine care. On average, nurses rated all procedures as being performed with pharmacologic analgesic only rarely. Physicians similarly rated all procedures as rarely performed with analgesics, with the exception of chest tube insertion and cutdowns, which were believed to often be performed with analgesics. Comfort measures were believed to be used substantially more than pharmacologic treatments, although on average no procedure was rated as usually performed with comfort measures. Both nurses and doctors believed that pharmacologic and non-pharmacologic pain-relieving therapies should be used in conjunction with painful procedures more frequently.

Although the discomfort experienced by early painful conditions may be transient, these experiences mould the nervous system to increase pain sensitivity both during early development and with maturity. This review will describe both animal and human studies that demonstrate the profound impact from early perinatal painful experiences. These studies support increased focus on perinatal pain incidents and the role of neuroplasticity in chronic pain.

Animal studies

Myelinated A-delta and unmyelinated C fibres transmit nociceptive impulses to the dorsal horn, which acts as an important sensory processing station and relay centre. In adult animal studies, peripheral injury results in changes in synaptic transmission within the dorsal horn that may set the stage for prolonged increased pain sensitivity, resulting in increased risk for chronic pain syndromes. The most widely accepted animal chronic pain model is the partial sciatic nerve ligation rodent [7, 8]. After exposing the sciatic nerve, a temporary ligature is tied around the nerve and later removed. Although the nerve heals and regains neurological function, the rat displays persistent pain behaviours by biting at the previously injured limb. In addition to behavioural changes, autopsy of those rats developing chronic pain behaviours shows widespread neurological changes, with re-wiring in the dorsal horn, spine and brain [9, 10]. For example, second-order neurons in the dorsal horn show increased sensitivity with increased action potentials and spontaneous discharges. Central terminals of mechanoreceptors re-distribute within the dorsal horn to connect with pain pathway neurons that would normally be triggered by pain stimuli. Furthermore, neuronal receptive field size increases. These dorsal horn changes are believed to result in a variety of well reported pain perception changes: increased sensitivity in the dorsal horn may lead to hyperalgesia; connection of mechanoreceptors to pain pathways may result in allodynia; and increased receptive field size may explain spread of pain beyond the borders of the initial area of injury.

A variety of studies have assessed the long-term consequences of perinatal pain stimuli in experimental animals. Several studies evaluating adult rats that were exposed to inflammatory or other noxious stimuli after birth are described below. In general, these studies show that perinatal pain results in increased pain sensitivity in mature rats, which may be at least partially explained by neural plasticity in the dorsal horn. These data suggest that pain exposure during the critical neonatal period when pain pathways are being developed will lead to long-standing increased pain sensitivity into adulthood.

Behavioural studies

Anand et al. [11] compared pain responses in adult rats that had been exposed from birth to day 7 to stimulation 4 times daily with needle sticks or a non-painful tactile stimulus. Tolerance to exposure to cold and hot plate testing was performed after the rats matured. Cold testing was similar for rats exposed to either needle sticks or tactile stimulus. Hot plate tolerance was significantly lower in rats that had received neonatal needle sticks *vs*. those receiving tactile stimuli when tested at ages 16 days (5.0 s *vs*. 6.2 s; $p<0.05$) and 22 days (3.9 s *vs*. 5.5 s; $p<0.005$). A recent study failed to confirm these earlier data [12]. In this study, newborn rats were similarly exposed to hindpaw needle stick four times daily, however, the control group was also exposed to a similar amount of handling and maternal separation as the needle stick group. In this study, there was a trend toward the needle stick group being more pain sensitive, with this difference achieving statistical significance only when differences in maternal grooming were also considered. These data suggest that positive maternal or comfort behaviour could ameliorate the effects of repetitive minor pain exposure in the newborn period.

Electrophysiology studies

The impact of neonatal pain on adult neuroanatomy and neurophysiology was tested in an experiment where an inflammatory agent or saline was injected into the hindpaws of newborn rats (days 0–3) [13]. Rats injected with the inflammation-provoking complete Freund's adjuvant showed pain behaviours post-injection and inflammation that persisted for 5–7 days. Saline-injected rats showed only immediate withdrawal to needle stick, with no additional pain behaviours or inflammation. Horseradish peroxidase labelling of dorsal horn primary afferents was increased by about 20% in the lower lumbar regions of the injected side in adult rats who had received neonatal inflammatory injections. Staining for calcitonin gene-related peptide was also increased in rats receiving inflammatory injections as newborn pups. Motoneuron labelling was similar in both limbs in both groups of adults. Horseradish peroxidase labelling was also tested in adult rats who had received an inflammatory injection on postnatal day 14. These rats demonstrated no change in neuronal staining. Possible clinical significance from this neonatal inflammation was demonstrated with physiological testing of mature rats, which revealed long-term behavioural consequences from neonatal pain exposure. Those mature rats that had received neonatal inflammatory injections showed an earlier display of the late phase of pain behaviour after formalin injection. Median time to late phase was 30.5 min in neonatally treated rats *vs*. 37.1 min in untreated rats ($p<0.02$), suggesting reduced neural inhibition or enhanced neural activation. In addition, adult rats exposed to neonatal pain showed increased dorsal horn neuron firing rates in response to brush and noxious pinch stimuli compared with untreated rats ($p<0.05$).

Torsney and Fitzgerald [14] similarly showed persistent changes in neurophysiology after neonatal exposure to a full thickness skin flap on the hindpaw. In this study, rat pups were subjected to injection with an inflammatory agent or skin flap. Extracellular recordings were made in the L4-5 dorsal horn cells after 3 and 6 weeks. Neither treatment changed spontaneous activity or mechanical thresholds. Rats receiving the skin flap injury exhibited increased spinal dorsal horn receptive field size by over 2 times ($p<0.01$).

Human studies

In humans, perinatal exposure to severe pain increases pain response in later infancy and adolescence. Taddio et al. [15] compared pain response to routine vaccination in boys at age 4–6 months, based on whether they had been circumcised or not. In this study, about 70% of all babies had been circumcised. Demographics were similar for circumcised and uncircumcised babies. After diphtheria-pertussis-tetanus vaccination, pain ratings were about 50% higher and cry duration was about 3 times longer (22 s *vs*. 7 s) for previously circumcised babies. Similarly, after Haemophilus influenzae B vaccination, pain scores were about 30% higher and cry duration about 3 times longer (53 s *vs*. 19 s) for previously circumcised babies.

In a later study, this same research group evaluated pain response to routine injection at 4–6 months in children who had post-delivery circumcision [16]. All of the babies had participated in a randomised, placebo-controlled clinical trial evaluating the use of Emla anaesthesia for circumcision. Pain response 4–6 months later to routine vaccination was measured by evaluating facial responses and cry duration, using standardised infant pain assessment measures. Demographics and overall temperament were similar in those babies previously circumcised with or without anaesthesia. Pain responses, as interpreted by both facial action and cry duration, were about twice as high in the infants previously circumcised without anaesthesia ($p<0.05$).

Pain sensitivity in adolescents has also been linked to perinatal pain experiences. A case-controlled study compared tenderness in 60 adolescents who had been born prematurely and treated in a neonatal intensive care unit (NICU) with adolescents born full-term [17]. Eighteen areas identified as typically tender in fibromyalgia patients were used as test locations for tenderness. In addition, 9 tender points and 4 control points were also tested for dolorimetry threshold, using a range of 0–9 kg pressure. Adolescents born prematurely reported significantly more tender areas (6.0 *vs*. 3.3; $p=0.001$) and lower threshold for both tender points (4.2 kg *vs*. 4.8 kg; $p=0.04$) and control sites (6.3 *vs*. 7.0; $p=0.02$). This difference was maintained after controlling for gender.

A recent retrospective chart review of paediatric migraineurs compared childhood migraines in children treated as newborns in a NICU or not [18]. As expected, children treated in a NICU experienced more early pain procedures and received more perinatal pain medications. Interestingly, the onset of paediatric migraine occurred earlier in those previously treated in a NICU (age 7.8 *vs*. 9.7 years; $p<0.01$). NICU-treated children also had a greater likelihood of being treated with daily prophylactic medication for migraine, with preventive therapies used for about 65% previously treated in a NICU *vs*. 25% with no NICU exposure. While these data must be interpreted with caution, they do suggest that early painful experiences may change nociceptive pathways, resulting in earlier onset and more frequent or recalcitrant migraines.

In each of these studies, perinatal pain exposure did not result in the development of an unprovoked chronic pain syndrome. Early pain, however, does seem to increase pain sensitivity in those children exposed to painful conditions, including routine vaccinations, tender point assessments or migraine.

Discussion

Even though children and adults do not have conscious memories of painful events occurring during the perinatal period, the nervous system apparently does "remember" those events by altering nociceptive pathways to increase pain sensitivity. Review of animal and human studies on the effects of perinatal pain supports the need for better implementation of analgesic care of newborns, particularly those exposed to repeated painful procedures. These studies also suggest that understanding chronic pain syndromes in adults may begin by better understanding how early pain exposures modify nociceptive pathways and pain sensitivity.

The cumulative effect of lifetime pain experiences on current pain perception was evaluated in 49 undergraduate volunteers [19]. Consistent with gender studies of pain tolerance to experimental pain [20], males in this study similarly showed a higher pain tolerance, with pain tolerance time 1.75 times longer in males. In addition, females rated their lifetime pain experience level over twice as high as the males. A linear relationship was established for both genders between lifetime pain experience and pain tolerance. These data further support that early pain experiences may affect later pain perception and tolerance.

Clinical recommendations

Consensus recommendations have been developed to provide guidelines for analgesic care in newborns [21, 22]. First, the staff caring for newborns need to be educated that procedures that would be painful in adults will also be painful for newborns, including premature babies. Painful procedures should be minimised in newborns. For example, venipuncture by trained staff is generally less painful than the more commonly performed heel lancing. In addition, line placement may be preferred in newborns requiring frequent venous access or injections. Non-invasive measures, such as pulse oximetry, should be maximised to reduce painful monitoring procedures. As in adults, sedation may blunt external pain behaviours in newborns without providing adequate analgesia. Comfort measures and analgesia should be considered for necessary painful procedures.

A wide variety of analgesic therapies are effective in newborns, including both non-pharmacologic and pharmacologic therapies [23]. Swaddling and sucrose administration via a pacifier are beneficial for most procedures [22, 23]. Both sucking and sucrose administration alone offer analgesic benefits, with benefits enhanced by combining both together [24]. Other sweet liquids, such as mother's milk, will also provide analgesic benefit. Topical anaesthetics should be considered for venipuncture/injections, line placement, lumbar punctures and circumcision [22]. Additional medications, including non-opioid and opioid analgesics may also be considered for other painful procedures, such as intubation, suctioning and chest tube insertion.

In a recent survey, painful procedures were prospectively logged over a 6-month period for all neonates during their first 14 days of admission in a NICU [25]. A total of 151 newborns were followed, with a mean NICU stay of 9 days. Newborns received an average of 14 procedures daily in the NICU. Most procedures were rated as moderately to severely painful by the treating staff. Despite the frequent exposure to painful procedures, use of analgesia was low. Less than 35% of newborns received analgesics each day. A total of 40% of newborns received no analgesia during their entire NICU stay. Furthermore, failed procedure rates were very high in this sample (Fig. 1), resulting in high exposure to repeated painful procedures.

Consensus guidelines recommend implementing educational programmes to increase the skill level of staff performing procedures on newborns to minimise pain and

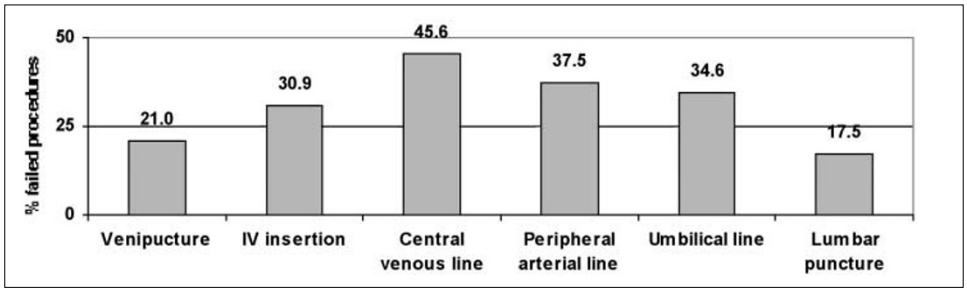

Fig. 1 Procedure failure in an NICU (based on Simons et al. [25])

the need to repeat failed procedures [21]. The high procedure failure rate for a wide range of frequently performed procedures in the NICU procedure survey [25] supports the need to train designated staff to develop an expertise in neonatal procedure administration. Use of comfort measures should also be encouraged, particularly in light of the recent study showing pain sensitivity in mature rats could be attenuated in newborn pups exposed to repeated pain with good maternal grooming [12].

The benefits of comfort and analgesia were reported in a brief report evaluating pain response at 8 months of age in low birth-weight babies who had previously been treated in a NICU [26]. Pain response was altered in 8-month-old babies who had been exposed to more invasive procedures ($p<0.001$). In addition, both maternal responsiveness ($p=0.006$) and greater use of morphine during the NICU stay ($p=0.03$) each independently predicted a more normal pain response at 8 months.

Future research

Better understanding of the neurophysiological consequences of pain exposure in the developing nervous system may broaden our understanding of how the nervous system may adapt after trauma or other noxious insult in older children and adults. In addition, animal perinatal pain models may provide a unique opportunity to evaluate the effects of pre-emptive analgesia. Pre-emptive analgesia has been evaluated in several operative models, using both opioid and non-opioid analgesia [27–29]. These studies have raised important questions about the best type of pre-emptive medication (opioid *vs*. non-opioid), route of administration and timing of delivery before painful insult. Many of these questions may be carefully studied using animal perinatal pain models by evaluating both anatomical and behavioural consequences of different pre-emptive administrations.

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