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Pain perception development and maturation

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Summary Newborn infants are not small adults. The pharmacokinetics and dynamics of analgesic drugs are immature at birth. Volumes of distribution, drug clearances, side-effects and drug efficacy all differ in newborns as compared to adults. Interestingly, these parameters develop before birth and during the postnatal period, reaching adult values after a period of months or years. This means that clinicians should anticipate on pharmacokinetic/pharmacodynamic (PK/PD) changes in newborns with increasing postconceptual age. The ability to perceive pain might also be immature at birth. Lower pain thresholds due to the absence of inhibitory descending spinothalamic fibers and a not yet fully developed cortical pain memory system are points of interest for our understanding of differences in pain perception in the newborn infant. Although this is a relatively unexplored area of research in humans, we will discuss the maturation and development of neonatal pain experience and perception in this paper.

Introduction

Pain and analgesic treatment in newborn infants have been studied intensively over the last few decades. It has taken several years to convince the medical world that nociception and pain experience are phenomena that are already apparent in newborn infants. Today, pain assessment and treatment should be part of current standard medical care in this vulnerable population.

The decision to use analgesics depends on the consequences of painful experiences in the newborn. In other words, if neonatal pain is harmful and causes negative effects in the newborn infant, it should be treated. For this reason, research has concentrated on the development of animal models to study the neurobiological substrate and development of pain experience in newborns and to study the short- and long-term consequences of these pain experiences.[1–3] Others have tried to show the negative effects of human neonatal pain experience on the long-term perspective.[4–6]

As the decision to treat neonatal pain also depends on the negative consequences of pain treatment, such as side-effects of analgesics, research has also concentrated on creating optimal treatment options for neonatal pain. Non-pharmacological strategies, such as the use of sucrose solutions for painful procedures have been extensively tested and implemented.[7] Whereas common analgesics such as paracetamol (acetaminophen), non-steroidal anti-inflammatory drugs (NSAIDs), morphine, and fentanyl have been investigated in randomized controlled clinical trials,[8–11] recent trials studying new drugs [e.g. intravenous

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paracetamol (acetaminophen)] show promising results for neonatal analgesia.[12,13] Preventing the effects of tolerance and addiction following the use of opioids is an increasing matter of concern at a time when very few data are available.

Despite this increase of knowledge about neonatal pain and improvements of neonatal pain treatment, clinical treatment of newborns is still related with frequent pain experiences without adequate analgesic pharmacological therapy.[14–16] Apparently, clinicians working in neonatal intensive care units feel that there is still not enough evidence of the necessity and efficacy of analgesic treatment in newborns. On the one hand, animal studies provide data about sedatives and anesthetics triggering widespread apoptotic neurodegeneration in the developing brain.[17] These data underline the possible dangers of drug use during the neonatal period. On the other hand, the results from animal studies must be very cautiously translated to the human newborn.[18] Where negative effects of, for instance, midazolam on neurological outcome are acknowledged in human trials, no evidence of such effects for many other agents is currently available.[19]

Clinical trials provide data that side-effects of analgesics might be apparent but of limited danger in the continuously monitored and ventilated newborn infant. Analgesic effects of opioids in ventilated newborns are hard to measure or even absent.[10,11] Apparently, the proved benefits from analgesic treatment often do not outweigh the fear for their side-effects. Lack of objective ways to measure pain and a large interindividual variability in pain behavior, as well as in the analgesic effects of drugs, add to this. The difficult challenge to find the best ways to treat neonatal pain, with maximal analgesia and minimal side-effects on the short- and long-term perspective, remains. Before analgesic treatment and ways of pain measurement are discussed, we here describe what is known about neonatal nociception and about the neonate's ability to actually feel and remember pain.

Nociception

The functional signaling pathways involved in the pain experience of newborn infants differ from those of adults. The immature nervous system develops from early gestation and continuous to change postnatally. Fig. 1 shows the anatomical and functional development of nociception and pain perception pathways. Nociception is the activity produced in the nervous system by noxious (potentially tissue-damaging) stimuli, e.g. the detection of a noxious event. Nociception involves peripheral sensory receptors—nociceptors—whose afferent fibers synapse in the spinal dorsal horn. During maturation, C-fiber projections are the last group of primary afferents to enter the dorsal gray matter, after proprioceptive and low-threshold A fibers. By 30 weeks, nerve tracts—probably those also involved in nociception—are myelinated up to the thalamic level (see Fig. 1). Afferent neurons in the thalamus project axons migrating into the neocortex. Synaptic connections of these thalamocortical tracts might occur at 24 weeks gestation. Reviewing the literature, Lee et al. recently concluded that direct thalamocortical fibers that are not specific for pain begin to emerge between 21 and 28 weeks' developmental age (23 and 30 weeks' gestational age).[20] In contrast to direct thalamocortical fibers, which are not visible until almost the third trimester, thalamic afferents begin to reach the somatosensory subplate at 18 weeks' developmental age (20 weeks' gestational age)[21] and the visual subplate at 20–22 weeks' gestational age.[22] These afferents appear morphologically mature enough to synapse with subplate neurons,[23] although no human study has shown that functional synapses exist between thalamic afferents and subplate neurons. The development of the

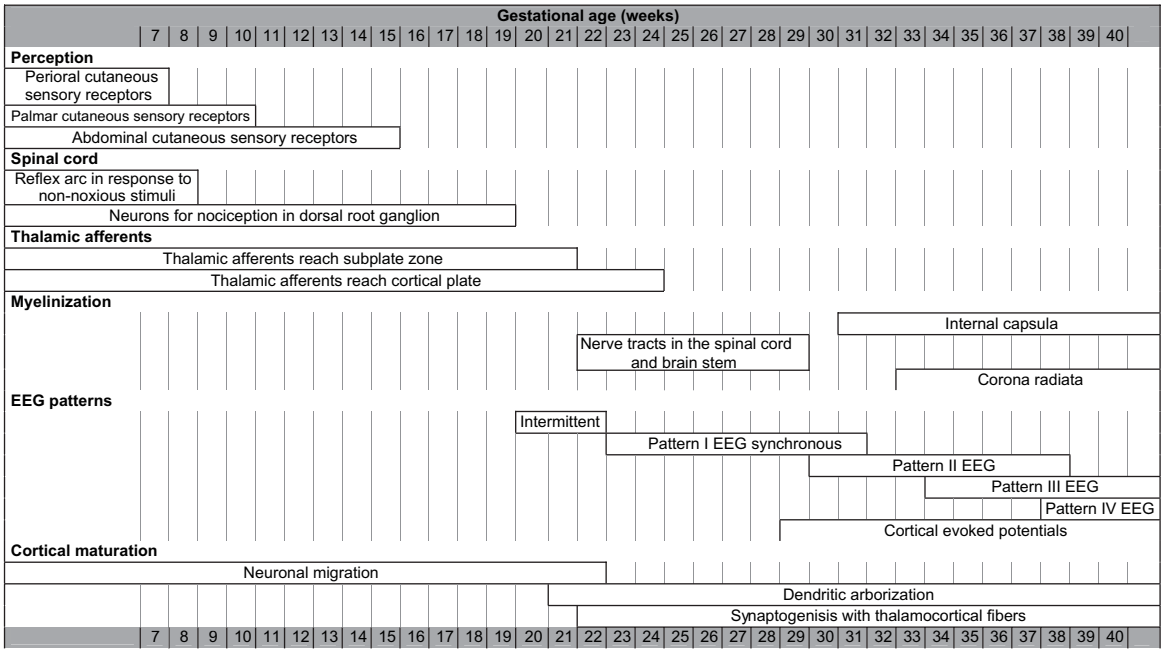

Figure 1 Anatomical and functional development related to pain perception (adapted from Lee et al.[20] and Anand and Hickey[45]).

fetal neocortex reaches the full complement of 10^9 neurons at around 20 weeks of gestation.[24] However, no human studies have directly examined the development of thalamocortical circuits associated with pain perception. The developmental age at which thalamic pain fibers reach the cortex has been inferred from studies of other thalamocortical circuits, which might or might not develop at the same time as thalamic fibers mediating the cortical perception of pain.

Recently, in an elegant review, Fitzgerald stated that most pain responses in preterm infants below 32 weeks, including facial expressions, seem to be largely subcortical.[25] If so, pain behavior in these premature newborns is importantly regulated by reflexes and the cortical pain 'experience' is probably minimal. These suggestions are based on a study of Oberlander et al., who showed that preterm neonates with and without parenchymal brain injury had comparable facial pain scores (so called NFCS scores) and heart rate variability at 32 weeks gestation.[26] Large changes in pain responses might be expected from these severe brain injuries if the neonatal cortex is importantly involved in pain responses. However, pain experience and pain response are not the same. In other words, although the response to a pain stimulus might—importantly—be regulated in the spinal cord and brainstem, this does not necessarily mean that the stimulus does not reach the neonatal cortex. Unfortunately, no cortical activity was measured in the study by Oberlander et al., for instance by the use of EEGs or near infrared spectroscopy. No data are available about the expected difference in pain responses of former preterm born newborns with and without brain injury at older ages when cortical involvement in pain response is apparent. In the coming years, these data will become available as longitudinal data from the NEOPAIN trail and a Dutch randomized controlled trial emerge.[10,11] Currently, evidence is lacking about the actual involvement of the preterm neonatal cortex in nociception and pain responses.

The neonate's ability to feel pain

Several arguments support the idea that neonates, even the most premature, are able to feel pain. Pain is a complex experience that involves not only the transduction of noxious stimuli (nociception) but also cognitive and emotional processing by the brain. Pain consists of sensory—discriminative, affective—emotional and cognitive—interpretational components, suggesting that a certain stage of development in the cortex is required to experience painful stimuli.[27] Neurophysiological afferent pain pathways reach the cortex between 20 and 26 weeks.[21,28] Although changes in pain behavior with gestational age can be found, even very prematurely born neonates show behavioral and physiological reactions and hormonal stress responses to painful stimuli.[29–32] As spinal reflexes cannot explain these reactions, the central nociceptive pathways, including spinothalamic and cortical fibers, must be already present in the very prematurely born neonates.

Supraspinal pain processing in the developing brain is still relatively unexplored. Evoked potentials signaling the arrival of sensory impulses at the cortex can be detected from 29 weeks of gestation.[33] Data about neurotransmitters and neuroanatomical areas suggest that the pain system undergoes a major reorganization during the perinatal period of life.[34] Imaging techniques, such as functional magnetic resonance imaging or positron emission tomography, have made visualization of cortical activity after painful stimuli possible. There is no 'pain center' as such in the brain, but studies in adults have showed that, during painful experiences, enhanced activity can be noted in the anterior cingulate, the thalamus, the lentiform nucleus, and the insular and prefrontal cortex, as well as in the primary and secondary somatosensory cortices.[35] Comparable studies in neonates would provide more understanding of the developing pain system. At present, the evidence about the premature neonate's capacity to experience pain is not yet conclusive.

Neonatal pain memory and long-term effects

When observing an 'uncomfortable' neonate it is hard to decide whether the behavioral discomfort is caused by pain, hunger or fatigue. The other way round, the neonate might not be able to discriminate between these emotions. It is not known whether a premature newborn even has the ability to remember pain. Memories for early painful events might not be accessible to explicit memory (conscious recall), although they are probably incorporated in the implicit memory that operates at the level of conditioning without awareness, coded by structural or functional changes within the pain system and other neuronal assemblies.[36] In the spinal cord the excitation of the synaptic connection between Aδ- and C-fibers and dorsal neurons shows lowered thresholds after repetitive stimulation, the so-called wind-up phenomenon. Furthermore, as receptive fields of adjacent dorsal neurons are overlapping, repetitive painful stimuli also cause spatial summation, causing hyperalgesia and allodynia.[37] This plasticity is probably caused by activation of the glutamate *N*-methyl-D-aspartate (NMDA) receptors after repetitive activation of nociceptors.[38]

Although the pain itself might not be consciously remembered, it could affect the short- and long-term perspective, as is suggested in clinical studies.[39–42] Murine studies have shown that abnormal or excessive activity in the developing central nervous system, due to pain, might alter normal synaptic development. This could lead to changes in the somatosensory processing and neurobehavioral sequelae.[1,43,44] However, the degree and duration of induced inflammation in rat models seem to be much greater than those caused by 'normal' procedural interventions in human neonates. Other studies have shown that using lower doses of inflammation results in an acute, but reversible, spinal expansion.[2] One study showed decreased responses to painful stimuli at 32 weeks postconceptual age in former prematurely born neonates compared to neonates born after 32 weeks.[5]

The methodological drawback of human studies is that all prematurely born neonates will experience pain as part of their intensive care treatment. As a consequence, the

negative effects of pain in premature neonates can be compared only with those in healthy term-born controls or between neonates receiving analgesia or placebo treatment. No follow-up data evaluating the long-term effects of pain with and without analgesia are yet available of infants participating in a randomized placebo-controlled trial after birth.

Conclusions

The conclusions from a recently published review by Lee et al. of the available evidence for the ability of the fetus to feel pain should be translated with care to the immature, preterm-born neonate.[20] Lee et al. conclude that, because evidence about the presence of functional thalamocortical pathways before the third trimester is lacking, no maternal analgesia is necessary to treat fetal pain from abortions. The risks to the mother of analgesic therapy to treat fetal pain add to this. In preterm neonates, the situation is completely different. First, their gestational age is older, increasing the evidence that they indeed might feel pain. Second, analgesic therapy will no longer affect or damage the mother, and is easier to apply because a placental transfer is no longer necessary. Furthermore, possible negative long-term effects of untreated pain play an important role in the consideration about whether to treat neonatal pain.

As long as conclusive evidence about the neonate's ability to feel pain, as well as the long-term effects of neonatal pain experience, is lacking, ethical considerations require us to believe that neonates do experience pain. Therefore attempts should be made to alleviate neonatal pain and to minimize any adverse effects of analgesic treatment. In the late 1980s, many clinicians changed their minds about the treatment of postsurgical pain as a result of data from clinical trials that showed the benefits from adequate analgesic therapy.[45,46] To establish adequate analgesia during intensive-care treatment of the newborn, clinicians' opinions again need to be changed. In 2004, an FDA-/NIH-sponsored meeting brought together experts in the field of neonatal pain research. Among their conclusions, they agreed that huge gaps in our knowledge still exist and that these preclude the dissemination and acceptance of evidence-based clinical guidelines for analgesia in ventilated preterm and full-term neonates. For instance, missing data related to the safety and efficacy of currently used analgesic drugs are missing.[47] This suggests that much more research is needed to fill these gaps in our knowledge.

Practice points

- Although conclusive evidence about the newborn's capacity to experience actual pain is lacking, ethical perspectives require us to believe that neonates do experience pain.
- Neonatal pain should always be treated, for instance using non-pharmacological techniques.

Research agenda

- The application and development of modern imaging techniques, such as functional MRI, are necessary to measure neonatal pain experience and to study analgesia.
- Long-term effects of neonatal pain and pharmacological analgesic therapy should be evaluated.

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