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In Review

Long-Term Consequences of Neonatal Injury

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The maturation of the central nervous system's (CNS's) sensory connectivity is driven by modality-specific sensory input in early life. For the somatosensory system, this input is the physical, tactile interaction with the environment. Nociceptive circuitry is functioning at the time of birth; however, there is still considerable organization and refinement of this circuitry that occurs postnatally, before full discrimination of tactile and noxious input is possible. This fine-tuning involves separation of tactile and nociceptive afferent input to the spinal cord's dorsal horn and the maturation of local and descending inhibitory circuitry. Disruption of that input in early postnatal life (for example, by tissue injury or other noxious stimulus), can have a profound influence on subsequent development, and consequently the mature functioning of pain systems. In this review, the impact of neonatal surgical incision on nociceptive circuitry is discussed in terms of the underlying developmental neurobiology. The changes are complex, occurring at multiple anatomical sites within the CNS, and including both neuronal and glial cell populations. The altered sensory input from neonatal injury selectively modulates neuronal excitability within the spinal cord, disrupts inhibitory control, and primes the immune system, all of which contribute to the adverse long-term consequences of early pain exposure.

Conséquences à long terme d'une blessure néonatale

La maturation de la connectivité sensorielle du système nerveux central (SNC) est dictée par les intrants sensoriels propres aux modalités, en début de vie. Pour le système somatosensoriel, ces intrants sont l'interaction physique, tactile avec l'environnement. La circuiterie nociceptive fonctionne au moment de la naissance; cependant, une part considérable de l'organisation et du raffinement de cette circuiterie se produit en période postnatale, avant que la pleine discrimination entre intrants tactiles et nuisibles ne soit possible. Ce raffinement implique la séparation des intrants afférents tactiles et nociceptifs à la corne dorsale de la moelle épinière, et la maturation de la circuiterie inhibitoire locale et descendante. La perturbation de ces intrants en début de vie postnatale (par exemple, par une lésion des tissus ou un autre stimulus nuisible) peut avoir une influence profonde sur le développement subséquent et par conséquent, sur le fonctionnement mature des systèmes de la douleur. Dans cette revue, nous présentons l'impact d'une incision chirurgicale néonatale sur la circuiterie nociceptive, en ce qui concerne la neurobiologie développementale sous-jacente. Les changements sont complexes et se produisent à de multipes sites anatomiques du SNC, incluant des populations cellulaires à la fois neuronales et gliales. Les intrants sensoriels altérés par une blessure néonatale modulent sélectivement l'excitabilité neuronale de la moelle épinière, perturbent le contrôle inhibitoire, et préparent le système immunitaire, et tout cela contribue à des conséquences indésirables à long terme de l'exposition à la douleur précoce.

Neonates and infants who require major surgery or intensive care management are exposed to painful stimuli at a time when the developing CNS is extremely sensitive to changes in sensory experience.[1] Surgical interventions may also be required to treat complications associated with prematurity or congenital abnormalities, frequently with further staged repairs necessary throughout childhood. As our awareness of the plasticity of infant pain mechanisms has increased, an important question has arisen regarding permanent alterations in pain sensitivity and higher cognitive functioning that are not seen following the same injury at older ages.[1–3] Prolonged and currently irreversible sensitization of the pain system has been demonstrated in children following neonatal intensive care, with more marked change in those born pre-term or who also require surgery.[4,5] Sensitivity to noxious stimuli is increased,[4] and pain and perioperative analgesic requirements are greater, at the time of subsequent surgery.[6]

Beyond the complex but well-described influence of early injury on somatosensory processing, evidence is now accumulating that the long-term consequences are more sophisticated, and that cognitive and behavioural changes occur that go far beyond alterations in thermal and tactile processing.[3] Pioneering experiments by Grunau

and colleagues (see Ranger and Grunau,[3] with references therein) identified internalizing behaviours prevalent in children born pre-term, compared with full-term control subjects, that persisted into adolescence and beyond (see Spittle et al[7]). Here again, parsing the neurobiological mechanisms that drive these changes is confounded by the interactions of nociception and stress.

Reducing pain is an important but often unmet need in neonates requiring intensive care,[8,9] and the solution does not simply lie in adapting treatments established in older age groups. The efficacy and side effect profile of anesthetic and analgesic drugs differ in neonates, and crucially both pain and analgesia have been independently reported to impair neurodevelopmental outcome,[10,11] and evidence to guide clinical choice of the most effective, safe, and developmentally appropriate pain management for this vulnerable population is lacking.[12] It is imperative to understand how responses to nociceptive stimuli develop with ongoing postnatal CNS development; how does brain activity and structure change throughout postnatal CNS development in terms of pain processing? It is not clear how the brain responds to, and is altered by, neonatal painful events or how those changes underlie the various neurodevelopmental outcomes reported clinically, in terms of both future responses to painful stimuli and other cognitive processes.[2,3]

At birth, nociceptive pathways are functional, and consequently, painful episodes and (or) procedures produce physiological and behavioural nociceptive responses. However, both acute and long-term responses to noxious stimuli change with the progression of postnatal development and repeated noxious stimuli increase activity in spinal and cortical nociceptive circuits and progressively increase hyperalgesia.[13] In trying to comprehend the underlying mechanism, it is important to make the point that—rather than simply trying to isolate noxious stimuli—stress, illness, genetic factors, and environment must be considered. These contextual factors are extremely important, as they all influence the behavioural response to nociceptive stimuli. Such is the clinical situation; in the laboratory, it is possible to try and parse the neurobiological influence of noxious tissue damage on subsequent development, although it must be borne in mind that pain is an inherently stressful event. The NICU is a stressful environment, and children who experienced life in the NICU show alterations in pain processing.[5,14] Stress hormones in former preterm babies when at school age are predictable by neonatal pain-related stress.[10,15,16] Even minor tissue damage, such as a heel lance, will cause nerve damage. Such procedures are performed at a time of major ongoing development within the CNS, and is particularly sensitive to changes in sensory experience.

Abbreviations

CNS	central nervous system
NICU	neonatal intensive care unit
RVM	rostroventral medulla

Highlights

- Considerable development of somatosensory circuitry in the CNS occurs postnatally.
- Exposure to painful stimuli during a critical postnatal period can alter pain sensitivity to subsequent injury in later life.

Therefore, it is not surprising that in situations of altered sensory activity, such as in the NICU, there are prolonged alterations in sensory function.

Pre-clinical models of early pain allow us to control, to a degree, for some of the stressors associated with the clinical population. While it can be problematic to directly extrapolate rodent postnatal CNS development with human development, it is possible to correlate spinal cord development during the first postnatal week in rodents with the human preterm and initial neonatal period,[13,17] and as such the postnatal rodent provides an appropriate model for certain aspects of CNS function and development in the human preterm infant.

A confound in parsing the mechanism of neonatal injury–induced changes within the CNS is the superimposing of injury-induced neuroplasticity onto developmental plasticity. The result is more complex than simply early injury making future painful events more sensitive. Animal and human studies have shown that while increased pain responses may be evident if a subsequent injury is at the site of the initial neonatal injury, there is also a widespread baseline hypoalgesia across the rest of the body.[1,5] This suggests that while specific alterations in the pathway from periphery to brain may have been altered subsequent to the initial injury, there is something more complex occurring centrally. Accumulating evidence implicates changes in local excitatory and inhibitory circuitry in the spinal cord's neuroimmune interactivity, and the development of descending inhibitory tone from the brainstem all underlie long-term consequences of neonatal injury.

Modelling Long-Term Effects of Pain by Neonatal Surgery

Persistent alterations in pain sensitivity have been shown in numerous neonatal rodent injury models, and they vary depending on the type and severity of injury and the age at which it occurs.[1] Inflammatory, skin wounding, and nerve injury models vary in their persistent effects, confounding an assessment of their long-term impact. More consistent has been the plantar hindpaw incision model,[18,19] which is well established and has been verified to produce quantifiable and reproducible hyperalgesia at all postnatal ages.[17–21] Plantar incision produces acute hyperalgesia in neonatal and adult rats, but the hyperalgesic response to an adult incision is enhanced by a prior neonatal incision. Crucially, this only occurs during a specific critical postnatal time window of the first postnatal week and is not seen if the initial injury is performed at older ages.[17] As this enhanced

response to repeat surgery only occurs subsequent to neonatal incision, changes to the normal developmentally regulated processes in nociceptive pathways ongoing at the time of initial incision must be occurring that differ from changes following adult incision.

Postnatal Development of Nociceptive Circuitry

There is considerable organization and segregation of afferent input to the spinal cord from the periphery and the transduction of sensory information that will subsequently be recognized as tactile, thermal, or nociceptive. As such, the fine-tuning of the system, and in particular the segregation of tactile and nociceptive input occurs postnatally, owing, in part, to the requirement for modality-specific stimuli, that is, tactile experience. In the adult animal, the dorsal horn of the spinal cord is the first point of modulation in the CNS of sensory information from the periphery. The spinal cord is not simply a relay station faithfully conveying this input to higher centres in the brain, but rather a site of complex processing, and of nociceptive information in particular. In the neonatal cord, while this circuitry is functional, the unrefined connectivity is such that noxious stimulation does not produce the same activity in the neuronal circuitry as in the adult.[22] In the neonatal rodent cord, the central terminals of low-threshold tactile afferents and high-threshold nociceptive afferents are interspersed within the dorsal horn, blurring the distinction and consequently the discrimination of tactile and noxious input.[23] The low-threshold fibres slowly retract from the site of high-threshold input in an activity-dependent manner until fully segregated after a few weeks of life.

Spontaneous activity is essential to the development of all sensory systems, the maturation of which is activity-dependent. The visual system requires light for the full maturation of the complex array of connectivity between retina and visual cortex and separation of eye-specific input,[24] and the same applies to other sensory systems, and in each case the activity required is sensory modality specific. To expedite the initial stages of activity-dependent development, spontaneous so-called pacemaker neurons provide endogenous excitation.[25] The recently described pacemaker neurons in the developing spinal cord provide this spontaneous activity, and also receive input from high-threshold afferents, the combination of which may be important for the activity-dependent fine-tuning of spinal nociceptive circuitry.[23,26,27] The excitatory drive provided by pacemaker neurons may be of benefit by allowing spinal circuit refinement without requiring repeated noxious input from the periphery[26] in the normal situation. Pacemakers modulate neuronal activity, both sensory (nociceptive) and motor. Further, spontaneous muscle activity, in turn, creates skin movement that provides innocuous feedback to the developing dorsal horn, and may be involved in driving the refinement of ectopic A-beta fibres in the most superficial laminae, a necessary event for the normal development of the nociceptive withdrawal reflex.[28,29] Integration of sensory and motor systems in postnatal development is essential to encode the correct development of reflexes, and therefore appropriate responses to innocuous and noxious stimuli. However, changes to that input, such as following surgical injury, can affect the electrophysiological properties of dorsal horn neurons, including pacemakers, reducing their intrinsic excitability into adulthood. The effects of this on postnatal developmental refinement of dorsal horn connectivity are as yet unknown, but the level of pacemaker activity is highly responsive to sensory experience.[26]

Descending Control

In addition to the local circuitry in the spinal dorsal horn, modulatory networks in the brain are constantly active in controlling adult spinal nociceptive activity. In essence, a feedback loop to dampen or enhance spinal activity in response to input from higher brain regions, including the limbic system and hypothalamus relaying activity associated with arousal and attention, the source of this descending input is the rostroventral medulla in the brainstem. In the mature CNS, both pro-and antinociceptive pathways lead directly from the RVM to the dorsal horn of the spinal cord. However, in early postnatal life, these descending pathways are almost exclusively facilitatory and targeted to low-threshold input.[30] The descending inhibitory control to the spinal cord is much slower to develop, during the course of the first 4 postnatal weeks in the rodent,[31,32] and is selectively targeted to high-threshold input.[30] Therefore, descending input from the RVM serves entirely different functions in early postnatal and adult animals. In the neonate, the descending facilitatory tone on low-threshold afferent input will act to promote the ongoing activity-dependent development and refinement of dorsal horn nociceptive circuitry. In addition to low-threshold afferent input being predominant in the neonatal dorsal horn, inhibitory tone is weak.[33] Activity, in terms of sensory influence from the physical environment, provides tactile and noxious input in postnatal life and drives the maturation of high-threshold connectivity and synaptic transmission in the spinal dorsal horn[34] (in addition to endogenous pacemaker activity), which, in turn, drives glycinergic inhibitory maturation.[35] The implications for early pain exposure are 2-fold: first, endogenous spinal inhibitory tone is reduced and less effective, in humans potentially throughout childhood and into early adolescence[36]; and second, the balance of descending facilitation and inhibition may be disrupted. This is supported by evidence that neonatal hindpaw inflammation leads to long-term alterations in supraspinal circuitry and increased descending inhibition.[37] The impact of early injury on this temporally regulated descending control of the developing and reorganizing dorsal horn requires further investigation.

Long-Term Effects of Early Injury on Spinal Nociceptive Circuitry

Neonatal surgical incision produces developmentally regulated and long-term changes in synaptic signalling within the spinal cord, with a net increase in excitatory drive owing to increased excitatory and decreased inhibitory synaptic signalling.[38–41] The increase in afferent input that results from neonatal surgical injury has direct effects on the

spinal dorsal horn neuronal excitability. Most dorsal horn neurons are interneurons, either excitatory or inhibitory, that process nociceptive input to the spinal cords in a way that remains not entirely understood in the adult animal. A very few dorsal horn neurons are projection neurons and transmit spinally processed sensory information to the brain. The balance of local interneuronal inhibitory and excitatory activity (in parallel with descending input) in spinal circuits is imperative to normal tactile and nociceptive processing, and perturbations in the circuitry can alter the output of projection neurons to higher centres in the CNS. Hindpaw surgical incision, again only during a critical period of postnatal plasticity, selectively increases excitatory synaptic drive in the dorsal horn.[40] The same injury, when performed in the neonatal period, decreases inhibitory transmission through a reduction in the inhibitory glycinergic input onto the spinal dorsal horn neurons in the adult.[41] Therefore, the functional organization of adult nociceptive circuitry is permanently changed by surgical incision in the neonate. In addition to these changes in synaptic connectivity in the adult dorsal horn following neonatal injury, there is also a long-lasting dampening in the intrinsic firing properties of the spinal dorsal horn neurons.[39] In essence, the membrane properties of dorsal horn neurons are shaped by sensory experience during early postnatal development.

Neuroimmune Interactions

It is important to emphasize that neuronal function is not something that occurs in isolation in the CNS, and specifically, the sensitivity of nociceptive pathways is not simply a product of neuron–neuron signalling. Neuronal activity occurs within the influence of the cellular milieu of the parenchyma, including elements of the immune system and, in turn, its activity influences the immune system. While transmission of nociceptive information from the spinal dorsal horn to the brain is a neuronally mediated process, the processing and modulation of that nociceptive signal within the dorsal horn involves interaction with the immune system. Within the CNS, the effector cells of the immune system are microglia, and, in the adult, these are generally considered reactive cells, capable of mounting anti- or proinflammatory responses to injury or disease.[42,43] Following peripheral nerve injury, microglia are a key cellular mediator of neuropathic pain in adult animals,[44–46] adopting a reactive phenotype in response to the injury. However, the immune system is also intimately involved in the development of the CNS, and recently, new roles for microglia have been elucidated that show that far from being merely reactive to injury or disease, they are instructive in synaptic maturation and elimination and plasticity.[47–49] Elements of these roles are likely crucial to the postnatal development of spinal nociceptive circuitry; for example, refinement and removal of inappropriate axons and synapses in the superficial dorsal horn. It is important to be biased toward driving this key developmental role before the more characteristic immune (and pronociceptive) role of the adult system to prevent the risk of autoinflammatory responses to normal developmental debris clearance.[50]

Neonatal surgical injury primes the spine's neuroimmune response,[51] and when performed within the critical postnatal period, enhances the degree and duration of subsequent injury-induced hyperalgesia, which is mirrored by changes in microglial reactivity in the spinal dorsal horn. Abolition of both these effects by administration of the glial-inhibiting tetracycline minocycline at the time of the second injury provides a functional role for microglia in the priming effect.[51] The molecular basis for this pain memory remains unclear, but microglia have been reported to retain an innate immune memory,[52] and, as they persist in the parenchyma for potentially the lifetime of the animal, may indeed have the ability to remain primed ready to be challenged again.[43,53]

Conclusion

Persistent postsurgical pain occurs both in adults and children. There are several contextual factors that influence and predispose long-term consequences of early injury, and age is of paramount importance. Injury during the critical period of plasticity has the potential to have far-reaching consequences on subsequent normal activity-dependent developmental processes. In the NICU, to improve survival, there is a requirement for potentially tissue-damaging procedures and repeated procedures to neonates. In most cases, very little can be done to limit the number of procedures, and greater knowledge of the impact of them on immediate and long-term development of the CNS as a whole is critically important. There is an urgent need to better understand interactions between neonatal surgical injury, pain, and cognition, to inform mechanism-based therapy and to improve long-term health and well-being. This review has presented evidence supporting that complex pain-sensing systems are present in neonates and that the usual pain inhibitory systems present in adults are not yet fully developed. This leaves neonates at higher risk of experiencing more acute pain from tissue-damaging procedures, such as needlestick or surgery. In addition, these systems are undergoing a critical period of rapid development, with the potential to affect long-term responses to noxious stimuli and, owing to neuroimmune interactions, may increase the risk of autoimmune responses.

Looking to the future, early injury is likely predictive of increased pain responses in later life, and it is critically important to assure appropriate pain assessment and management during this period.

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