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SPECIAL ARTICLE

PAIN AND ITS EFFECTS IN THE HUMAN NEONATE AND FETUS

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THE evaluation of pain in the human fetus and neonate is difficult because pain is generally defined as a subjective phenomenon.[1] Early studies of neurologic development concluded that neonatal responses to painful stimuli were decorticate in nature and that perception or localization of pain was not present.[2] Furthermore, because neonates may not have memories of painful experiences, they were not thought capable of interpreting pain in a manner similar to that of adults.[3-5] On a theoretical basis, it was also argued that a high threshold of painful stimuli may be adaptive in protecting infants from pain during birth.[6] These traditional views have led to a widespread belief in the medical community that the human neonate or fetus may not be capable of perceiving pain.[7,8]

Strictly speaking, nociceptive activity, rather than pain,should be discussed with regard to the neonate, because pain is a sensation with strong emotional associations. The focus on pain perception in neonates and confusion over its differentiation from nociceptive activity and the accompanying physiologic responses have obscured the mounting evidence that nociception is important in the biology of the neonate. This is true regardless of any philosophical view on consciousness and "pain perception" in newborns. In the literature, terms relating to pain and nociception are used interchangeably; in this review, no further distinction between the two will generally be made.

One result of the pervasive view of neonatal pain is that newborns are frequently not given analgesic or anesthetic agents during invasive procedures, including surgery.[9-12] Despite recommendations to the contrary in textbooks on pediatric anesthesiology, the clinical practice of inducing minimal or no anesthesia in newborns, particularly if they are premature, is widespread.[9-12] Unfortunately, recommendations on neonatal anesthesia are made without reference to recent data about the development of perceptual mechanisms of pain and the physiologic responses to nociceptive activity in preterm and full-term neonates. Even Robinson and Gregory's landmark paper demonstrating the safety of narcotic anesthesia in preterm neonates cites "philosophic objections" rather than any physiologic rationale as a basis for using this technique.[10] Although methodologic and other issues related to the study of pain in neonates have been discussed,[13-15] the body of scientific evidence regarding the mechanisms and effects of nociceptive activity in newborn infants has not been addressed directly.

Anatomical and Functional Requirements for Pain Perception

The neural pathways for pain may be traced from sensory receptors in the skin to sensory areas in the cerebral cortex of newborn infants. The density of nociceptive nerve endings in the skin of newborns is similar to or greater than that in adult skin.[16] Cutaneous sensory receptors appear in the perioral area of the human fetus in the 7th week of gestation; they spread to the rest of the face, the palms of the hands, and the soles of the feet by the 11th week, to the trunk and proximal parts of the arms and legs by the 15th week, and to all cutaneous and mucous surfaces by the 20th week.[15,16] The spread of cutaneous receptors is preceded by the development of synapses between sensory fibers and interneurons in the dorsal horn of the spinal cord, which first appear during the sixth week of gestation.[17,18] Recent studies using electron microscopy and immunocytochemical methods show that the development of various types of cells in the dorsal horn (along with their laminar arrangement, synaptic interconnections, and specific neurotransmitter vesicles) begins before 13 to 14 weeks of gestation and is completed by 30 weeks.[19]

Lack of myelination has been proposed as an index of the lack of maturity in the neonatal nervous system[20] and is used frequently to support the argument that premature or full-term neonates are not capable of pain perception.[7,10] However, even in the peripheral nerves of adults, nociceptive impulses are carried through unmyelinate (C-polymodal) and thinly myelinated (A-delta) fibers.[21] Incomplete myelination merely implies a slower conduction velocity in the nerves or central nerve tracts of neonates, which is offset completely by the shorter interneuron and neuromuscular distances traveled by the impulse.[22] Moreover, quantitative neuroanatomical data have shown that nociceptive nerve tracts in the spinal cord and central nervous system undergo complete myelination during the second and third trimesters of gestation. Pain pathways to the brain stem and thalamus are completely myelinated by 30 weeks; whereas the thalamocortical pain fibers in the posterior limb of the internal capsule and corona radiata are myelinated by 37 weeks.[16]

Development of the fetal neocortex begins at 8 weeks gestation, and by 20 weeks each cortex has a full complement of 10^9 neurons.[23] The dendritic processes of the cortical neurons undergo profuse arborizations and develop synaptic targets for the incoming thalamocortical fibers and intracortical connections.[23,24] The timing of the thalamocortical connection is of crucial importance for cortical perception, since most sensory pathways to the neocortex have synapses in the thalamus. Studies of primate and human fetuses have shown that afferent

neurons in the thalamus produce axons that arrive in the cerebrum before mid-gestation. These fibers then "wait" just below the neocortex until migration and dendritic arborization of cortical neurons are complete and finally establish synaptic connections between 20 and 24 weeks of gestation (Fig. 1).[27-38]

Functional maturity of the cerebral cortex is suggested by fetal and a neonatal electroencephalographic patterns, studies of cerebral metabolism, and the behavioral development of neonates. First, intermittent electroencephalograpic bursts in both cerebral hemispheres are first seen at 20 weeks gestation; they become sustained at 22 weeks and bilaterally synchronous at 26 to 27 weeks.[39] By 30 weeks, the distinction between wakefulness and sleep can be made on the basis of electroencephalo- graphic patterns.[39,40] Cortical components of visual and auditory evoked potentials have been recorded in preterm babies (born earlier than 30 weeks of gestation),[39,40] whereas olfactory and tactile stimuli may also cause detectable changes in electroencephalograms of neonates.[39,42] Second, in vivo measurements of cerebral glucose utilization have shown that maximal metabolic activity in located in sensory areas of the brain in neonates (the sensorimotor cortex, thalamus, and mid brain- brain-stem regions), further suggesting the functional maturity of these regions.[43] Third, several forms of behavior imply cortical function during fetal life. Well-defined periods of quiet sleep, active sleep, and wakefulness occur in utero beginning at 28 weeks of gestation.[11] In addition to the specific behavioral responses to pain described below, preterm and full-term babies have various cognitive, coordinative, and associative capabilities in response to visual and auditory stimuli, leaving no doubt about the presence of cortical function.[45]

Several lines of evidence suggest that the complete nervous system is active during prenatal development and that detrimental and developmental changes in any part would affect the entire system.[35,36,42,46] In studies in animals, Ralston found that somatosensory neurons of the neocortex respond to peripheral noxious stimuli and proposed that "it does not appear necessary to postulate a subcortical mechanism for appreciation of pain in the fetus or neonate."[47] Thus, human newborns do have the anatomical and functional components required for the perception of painful stimuli. Since these stimuli may undergo selective transmission, inhibition, or modulation by various neurotransmitters, the neurochemical mechanisms associated with pain pathways in the fetus and newborn are considered below.

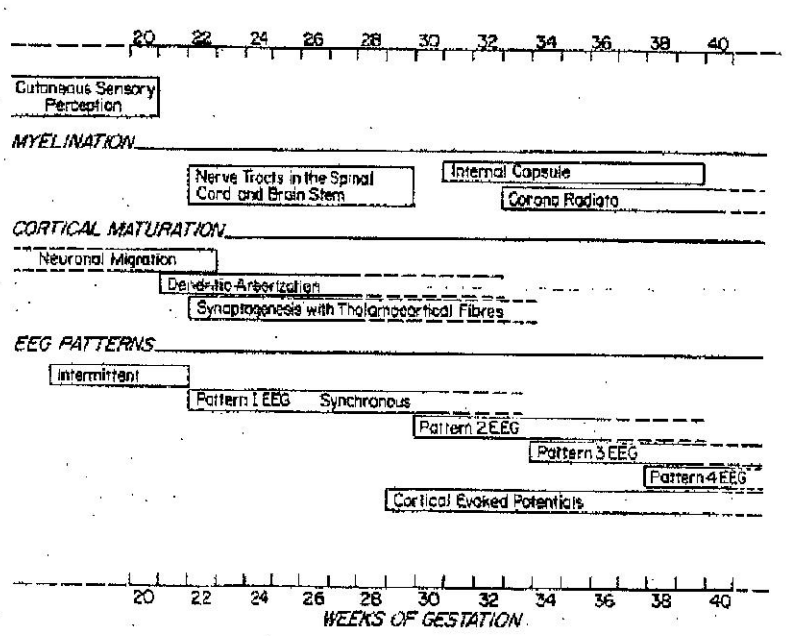

Figure 1. Schematic Diagram of the Development of Cutaneous Sensory Perception,[25] Myelination of the Pain Pathways,[32] Maturation of the Fetal Neocortex,[34-37] and Electroencephalographic Patterns[39-42] in the Human Fetus and Neonate.

Neurochemical Systems Associated with Pain Perception

The Tachykinin System

Various putative neurotransmitters called the tachykinins (substance P, neurokinin A, neuromedin K, and so forth) have been identified in the central nervous system, but only substance P has been investigated thoroughly and shown to have a role in the transmission and control of pain impulses.[19,20] Neural elements containing substance P and its receptors appear in the dorsal-root ganglia and dorsal horns of the spinal cord at 12 to 16 weeks of gestation.[37] A high density of substance P fibers and cells have been observed in multiple areas of the fetal bran stem associated with pathways for pain perception and control and visceral reactions to pain.[20,21] Substance P fibers and cells have also been found in the hypothalamus, mamillary bodies, thalamus, and cerebral cortex of human fetuses early in the development.[28] Many studies have found higher densities of substance P and it receptors in neonates than in adults of the same species, although the importance of this finding is unclear.[21,44-48]

The Endogenous Opioid System