Neurobiology of Acute Pain in Early Life

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Pain is a multi-layered phenomenon
◆Different types of pain: tissue injury, inflammation, nerve damage, visceral origin
◆Unique receptors and mechanisms used for different types of pain: specialized nociceptors, nerve fibers, DRG cells, processing in spinal & supraspinal areas
◆Sequential neurobiological changes follow acute pain: activation → modulation → modification of the pain system
◆Pain-related phenomena include: primary and secondary hyperalgesia, allodynia, temporal or spatial summation, sympathetically maintained pain, referred pain, pain of central origin

Pain System Activation
◆Activation of different peripheral nociceptors, serve as transducers for specific stimuli. For example:
–heat activates → VR1, VRL1
–mechanical pressure activates → mDeg ion channels
–chemicals like acids or ATP activate → ASICs, P2X3
◆Activation-dependent plasticity:
–Nociceptor terminals: Autosensitization
–Dorsal horn neurons: Wind-up and Central sensitization
–Primary, secondary, visceral hyperalgesia, allodynia

Modulation-dependent Plasticity
◆Nociceptors: Heterosensitization
─sensitizing agents: PGE_2, 5-HT, bradykinin, epinephrine, adenosine
─activation of PKA, PKC□ : PN3/SNS, VR1
◆Dorsal horn: Central sensitization
─homosynaptic, heterosynaptic
─AMPA, NMDA, CaMK-II
◆Receptor convergence:
─NK1, NMDA, NPY, mGluR1

Infants are more sensitive to pain
◆Lower pain thresholds in neonatal rat pups (Collier & Bolles, 1980; Fitzgerald et al, 1988; Falcon et al, 1996; Hu, Hu, Berde, 1997; McLaughlin et al, 1990; Teng & Abbot, 1998)
◆Delayed maturation of descending inhibition, which does not occur until after birth (Fitzgerald & Koltzenberg, 1986; Marti et al, 1990; Fitzgerald et al, 1998; Ren et a, 1997)
◆Infants and children develop prolonged windup and hyperalgesia (Fitzgerald et al, 1988; Andrews & Fitzgerald, 1999)
◆Consequently, infants show greater hemodynamic, immune, hormonal & metabolic stress responses (Anand et al, 1985; Anand & Aynsley-Green, 1988; McIntosh et al, 1994)

Epidemiology of pain

Porter & Anand, 1998

◆144 neonates:7,672 procedures
◆53 procedures / patient, 87% heelsticks
◆3% procedures preceded by analgesia

Simons, Tibboel, Anand, et al., 2003

◆N = 151 neonates over 14 days
◆Total 19,674 procedures, 31% repeats
◆196 / patient, 63% suctioning
◆VAS scores for moderate / severe pain
◆<35% procedures preceded by analgesia

Cortical activation following tactile and painful Stimuli
(Bartocci, Bergqvist, Lagercrantz, Anand, Pain 122: 109-117, 2006)

To study the patterns of supraspinal pain processing in neonates, we hypothesized that acute pain causes metabolic and haemodynamic changes associated with activation of the somatosensory cortex. Forty preterm neonates at 28-36 weeks of gestation (mean=32.0) and at 25-42 hours (mean=30.7) of age were studied following standardized tactile (skin disinfection) and painful (venipuncture) stimuli. Changes in regional cerebral haemodynamics were monitored by Near Infrared Spectroscopy (NIRS) over both somatosensory cortices in 29 newborns, and over the contralateral somatosensory and occipital areas in 11 newborns. Tactile stimulation produced no changes in HR or SaO2. HR increased in the first 20 seconds ($p<0.001$), while SaO2 decreased during the 40 seconds after venipuncture ($p<0.0001$). Following tactile or painful stimulation, [HbO2] increased bilaterally regardless of which hand was stimulated ($p<0.0001$). Pain-induced [HbO2] increases in the contralateral somatosensory cortex ($p<0.05$) were not mirrored in the occipital cortex ($p>0.1$). Pain-related [HbO2] increases were more pronounced in male neonates ($p<0.05$ on left, $p<0.001$ on right), inversely correlated with gestational age ($r= -0.53$ on left, $p<0.01$; $r= -0.42$ on right, $p<0.05$) and directly correlated with postnatal age ($r=0.75$ on left, $p<0.0001$; $r=0.67$ on right, $p<0.0001$). Painful and tactile stimuli elicit specific haemodynamic responses in the somatosensory cortex, implying conscious sensory perception in preterm neonates. Somatosensory cortical activation occurs bilaterally following unilateral stimulation and these changes are more pronounced in male neonates or preterm neonates at lower gestational ages.

Recent views on early development of pain

◆Lee, S. J., Ralston, H. J. P., Drey, E. A., Partridge, J. C. & Rosen, M. A. Fetal pain: A systematic multidisciplinary review of the evidence. JAMA 294: 947-954, (2005)
◆Mellor, D. J., Diesch, T. J., Gunn, A. J. & Bennet, L. The importance of 'awareness' for understanding fetal pain. Brain Research Reviews 49: 455-71, (2005)
◆Derbyshire, S. W. G. Can fetuses feel pain? British Medical Journal 332: 909-12, (2006)
◆Williams, C. Framing the fetus in medical work: rituals and practices. Social Science & Medicine 60: 2085-95, (2005)
◆Anand KJS. Fetal pain? Pain-Clinical Updates 14:1-4, (2006)

Mellor, et al. Brain Research Reviews 49: 455-71, (2005)
◆Review of the basic science literature related to fetal pain
◆Fetal responses to nociceptive stimuli → Suppressors of fetal behavior and cortical activity → Evidence for fetal sleep → Endogenous inhibition of fetal sensory perception
◆Conclusions: "The uncritical view that the nature of presumed fetal pain perception can be assessed by reference to the prematurely born infant is challenged. Rigorously controlled studies of invasive procedures and analgesia in the fetus are required to clarify the impact of fetal nociception on postnatal pain sensitivity and neural development, and the potential benefits or harm of using analgesia in this unique setting."

Derbyshire. British Medical Journal 332: 909-12, (2006)
◆Synthesis of published literature related to fetal pain
◆Neuroanatomy of pain pathways → fetal psychology → content of pain → mind developmental → Clinical and policy implications
◆Conclusions: "The neural circuitry for pain in fetuses is immature. More importantly, developmental processes necessary for the mindful experience of pain are not yet developed..... Avoiding a discussion of fetal pain with women requesting abortions is not misguided paternalism but a sound policy based on good evidence that fetuses cannot experience pain."

Fetal Pain: 3 major flaws in the scientific rationale used by Lee et al. (2005), Derbyshire (2006) and Mellor et al. (2005)
1. Pain is not a hard-wired system
2. The structures or mechanisms used for pain perception are different in fetal vs. adult life
3. Cortical activation/ablation does not alter pain perception

In addition, these studies have:
◆Serious methodological problems
◆Conflicts of interest

Williams. Social Science & Medicine 60: 2085-95, (2005)
◆Direct observation of abortions and other procedures
◆Interviews of medical & midwifery practitioners
◆Interviews nationally of lay people with specific perspectives on women and fetuses
◆Qualitative analysis of common themes and concepts
◆Fetal pain in reports & medical articles → Fetal pain in the clinical context → links with personhood?

Responses of the Fetus to Acute Pain
◆At 18-20 weeks gestation: fetal plasma noradrenaline, cortisol, and β-endorphin responses to needling (Partch et al 1991, Giannakoulopoulos et al 1994, 1999)
◆These stress responses are independent of gestation or the maternal hormonal response (Gitau et al 2001)
◆At 16 weeks gestation: pulsatility index of middle cerebral artery decreases and femoral artery increases, implying greater blood flow to brain (Teixeira et al 1999, Smith et al 2003)
◆At 20 weeks gestation: fentanyl reduces pain effects on fetal cortisol, β-endorphin, and the middle cerebral artery pulsatility index (Fisk et al 2001)

Why is this important?

- Because of fetal surgery being performed at many centers
- Because of the long-term effects of early acute pain on subsequent brain development
- Because of its implications for neonatal care in the NICU

Effects of handling on responses to acute pain
(Porter et al. Pediatrics 1998; 102: 1383-1389.)
◆RCT of preterm neonates handled (N=21) & not handled (N=27) before heelstick
◆Heart rate increased with handling but promptly returned to pre-handling levels
◆Handled group infants had: higher mean heart rate, greater arousal, more facial activity

Pain reactivity in Preterm Neonates
◆Physical handling increases their responses to heel lance (Porter et al., Pediatrics 1998)
◆More procedures in the previous 24 hr → increases response to tracheal suctioning (Grunau, et al., Clin J Pain 2000)
◆Heel lance increases facial and HR reactivity to routine nursing care (Holsti et al., 2005)

Hypersensitivity following acute pain: supraspinal mechanisms (Liu, et al., 2004)
Central nociceptive processing includes spinal and supraspinal neurons, but the supraspinal mechanisms mediating changes in pain threshold remain unclear. We investigated the role of forebrain neurons in capsaicin-induced hyperalgesia. Long-Evans rat pups at 21 days were randomized to undisturbed control group, or to receive tactile stimulation, saline injection (0.9% w/v) or capsaicin injection (0.01% w/v) applied to each paw at hourly intervals. Thermal paw withdrawal latency was measured 1 h later, forebrains were removed and purified forebrain neuronal membranes were assayed for adenylyl cyclase activity and opioid receptor function. Capsaicin-injected rats had decreased thermal latency ($P<0.0001$) compared to the other groups. Neuronal membranes showed increased basal ($P=0.0003$) and forskolin-stimulated ($P=0.0002$) adenylyl cyclase activity in the capsaicin group compared to other groups. The selective μ-opioid receptor agonist, DAMGO ([D-Ala^2, N-Me-Phe^4, Gly^5-ol]enkephalin) was less effective in inhibiting adenylyl cyclase activity in the capsaicin group ($P<0.001$) compared to other groups. These effects were naloxone-reversible and pertussis toxin-sensitive ($P<0.01$) in the control, tactile stimulation and saline injection groups but not in the capsaicin group. Binding capacity and affinity for μ̃opioid receptors were similar in all four groups, suggesting that receptor down-regulation was not involved. Exposure to DAMGO increased [^{35}S]GTPγS binding to neuronal membranes from the control, tactile, and saline groups ($P<0.001$) in a naloxone-reversible and pertussis toxin-sensitive manner ($P<0.01$) but not in the capsaicin group, suggesting μ̃opioid receptor desensitization. Dose responses to systemic morphine were also reduced in the capsaicin group compared to the tactile group ($P<0.05$). Capsaicin-induced hyperalgesia in 21-day-old rats was associated with an uncoupling of μ̃-opioid receptors in the forebrain. Opioid receptor desensitization in the forebrain may reduce opioidergic inputs to the descending inhibitory controls, associated with behavioral hyperalgesia and reduced responsiveness to morphine analgesia in capsaicin-injected young rats.

Hypersensitivity following acute pain: supraspinal mechanisms (Liu, et al., 2004)

◆Uncoupling of opioid receptors in the forebrain → less opioidergic tone → altered thalamic and brainstem processing of pain→ disinhibition of neurons in the dorsal horn →

- ◆hyperalgesic response to hot plate
- ◆decreased responses to morphine analgesia

Persistent hypersensitivity following acute pain
Abdulkader H, McIntosh N, et al. (unpublished data, 2005)
◆Preterm & term neonates stimulated with Von Frey hairs during the 1st yr
◆Flexion withdrawal reflex measures sensitivity of the C-fiber afferent limb
◆Thresholds for the flexion withdrawal reflex increased gradually in term neonates, but remained unchanged for preterm neonates during the subsequent 1 year of life.

Long-term effects of injury: rat pups
◆Increased peripheral nerve sprouting following neonatal skin wounds (Reynolds & Fitzgerald, 1995, 1997; De Lima et al, 1999)
◆Decreased receptive field size of dorsal horn neurons (Rahman et al, 1997)
◆Sprouting of sciatic primary afferents, increased excitability of dorsal horn neurons (Ruda et al, 2000)
◆Increased anxiety, greater alcohol preference, neophobia, hypervigilance behavior (Anand et al, 1999)
◆Altered pain thresholds, responses to morphine analgesia (Bhutta, Anand et al, 2001)