

## Annotations

# Pain and analgesia in the newborn

The traditional view that neonates do not feel pain is now being questioned. Early studies showed what was thought to be a decorticate response in babies with no localisation to painful stimuli and this, together with the belief that the painful experience was not remembered, implied that pain was unimportant.<sup>1</sup> As a consequence and because of certain anxieties about the handling of drugs (particularly opiates) in the newborn there has been a reluctance to prescribe analgesia for these patients.<sup>2</sup> Data now suggest that infants do feel pain.<sup>1, 3, 4</sup> In this review the underlying neurobiology of pain development in neonates is described, followed by a review of clinical studies indicating that the newborn baby responds (possibly adversely) to pain. We conclude that the arguments in favour of the use of analgesia have become overwhelming.

### Neurobiology of pain development

The limited evidence available shows that innervation of the peripheral tissue and the basic connections between primary sensory neurones and the cells in the dorsal horn of the spinal cord occurs early in fetal development. In this review we concentrate on those events that seem to occur later in fetal life or in the early postnatal period. In rats the central neurophysiological effects of unmyelinated C fibres, the group of afferents that are particularly concerned in chronic and inflammatory pain, mature gradually over the first two to three postnatal weeks.<sup>5, 6</sup> This maturation is associated with several anatomical and chemical changes. The concentrations of neuropeptides found within the C fibres (such as substance P, somatostatin, and vasoactive intestinal polypeptide) increase considerably during the early postnatal period.<sup>7</sup> Furthermore, at birth binding sites for substance P are in high concentrations and distributed diffusely over the grey matter, and only become defined in specific laminae and reduced in number as the rat matures.<sup>8</sup> Whether there is a similar delayed development of C fibres in man is not known, but there is a pronounced increase in the concentrations of the above neuropeptides around the time of birth.<sup>7, 9</sup>

The activity of interneuronal pathways in the dorsal horn, especially relevant to pain processing,

also develops postnatally. The spinal cord lacks inhibitory control at birth and although the synaptic linkage between afferents and dorsal horn cells is still weak, receptive fields are large and single stimuli can often evoke long lasting excitation that lasts for several minutes; repeated stimuli can build up considerable background activity in the cells.<sup>5</sup> The result is that otherwise weak cutaneous inputs are made more effective centrally. The flexor reflex, a useful measure of nociceptive function at the spinal cord level, is highly exaggerated in neonates.<sup>10, 11</sup> Thresholds are lower and the flexion withdrawal lasts longer. Repeated skin stimulation results in considerable hyperexcitability or sensitisation, which is particularly pronounced before 35 weeks' gestation in the human and the eighth postnatal day in rats.<sup>11</sup> Nevertheless there is a marked reduction in the threshold of this reflex after skin injury in the newborn that is analogous to the tenderness or hyperalgesia experienced in adults.<sup>12</sup> Inhibitory pathways descending from the brain stem are ineffective at birth,<sup>13</sup> perhaps because their neurotransmitters (5-hydroxytryptamine and noradrenaline) appear only postnatally.<sup>14</sup>

### Development of opioid sensitivity

Another important postnatal event is the maturation of the opioid/opiate system in the spinal cord. No analgesic effects of morphine can be detected in the rat pup until the seventh postnatal day and adult sensitivity is only reached at the 14th postnatal day, exactly coinciding with the appearance of high affinity mu-receptor binding in the rat cord. K-receptors and ketocyclazocine analgesia mature earlier at the seventh to 10th postnatal days.<sup>15</sup> Delta receptors develop last at the 12th postnatal day but the mu:delta ratio does not reach 1:1 until the 26th postnatal day.<sup>16</sup> Little is known about opiate receptor development in the human cord, but it apparently begins before birth. Morphine and other opioids are effective analgesics in newborn infants born both prematurely and at full term, although dose response studies have not been undertaken.<sup>1, 4</sup> Enkephalin appears postnatally (first postnatal day) in the rat and is found later than most other peptides in the human fetal dorsal horn at 12–14 weeks.<sup>17</sup>

**Assessment of pain in the newborn infant**

Three types of response to painful stimuli have been studied in the newborn human infant.

**AUTONOMIC RESPONSES**

Changes in heart rate, blood pressure, transcutaneous partial pressure oxygen, and palmar sweating are common autonomic responses to pain. In newborn babies, lancing of the heel produces sustained increases in heart rate in full term infants but the responses are less clear in the preterm baby.<sup>18</sup> The palmar sweating response to this stimulus does not appear until 37 weeks' gestation.<sup>19</sup> Local anaesthesia prevents the heart rate and blood pressure changes associated with circumcision.<sup>20</sup>

**BEHAVIOURAL RESPONSES**

Diffuse body movement and purposeful withdrawal have been quantified in response to painful stimuli<sup>21</sup> and have been used to show that the preterm infant is, if anything, supersensitive to painful stimuli when compared with the full term infant.<sup>11</sup> These responses can be reduced by local analgesia (M Fitzgerald, C Millard, N McIntosh, unpublished observations). Facial expressions have also been linked with painful stimuli but vary with the behavioural state.<sup>22</sup> Crying (? primitive communication) has been evaluated clinically and by spectrographic analysis. A painful cry is different from that indicating hunger or fear in a full term baby, but the differentiation is difficult in the preterm infant.<sup>23</sup>

**HUMORAL AND METABOLIC RESPONSES**

Anand *et al* studied the response to surgical operations in neonates.<sup>24</sup> A pronounced release of catecholamines, growth hormone, glucagon, aldosterone, and other corticosteroids was seen when insulin secretion was suppressed. These responses were associated with the breakdown of fat and the release of carbohydrates resulting in increased concentrations of glucose, lactate, pyruvate, ketone bodies, and non-esterified fatty acids in the blood, as well as an increase in the breakdown of protein.<sup>4</sup> Potent anaesthetic agents (for example, fentanyl and halothane) inhibited these stress responses<sup>25</sup> and preliminary data suggested that the stress response might be associated with increased post-operative morbidity and mortality.<sup>14</sup>

**Conclusions**

Laboratory studies have shown that the basic connections required for painful stimuli to be transmitted to the central nervous system are present in the newborn, despite the considerable organisation

and maturation (particularly of control systems) that occurs postnatally. Clinical studies of the pain responses mounted by newborn babies have confirmed that these pathways are functional, albeit somewhat variable. Furthermore, in some cases these behavioural changes persisted after the painful procedure, implying that the experience was remembered.<sup>26</sup> This behaviour may disrupt both the infants' adaptive responses to feeding and the mother/infant reactions.<sup>27</sup> Anaesthetic agents reduce the stress response after neonatal operations. It is difficult at this stage to evaluate whether a profound stress response is good or bad. Stability of physiology is important in the preterm infant: fluctuations of arterial oxygen pressure may be potentially dangerous to the eye,<sup>28</sup> and variability in blood pressure has been linked with the occurrence and extension of intraventricular haemorrhage.<sup>29</sup> The suggestion, however, that there are fewer side effects of operation when potent anaesthetic agents are used,<sup>24</sup> and that postoperative mortality and morbidity are reduced, mean that the judicious provision of analgesia is important, independent of whether the pain is remembered.

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M FITZGERALD

*Department of Anatomy and Developmental Biology,  
University College,  
London WC1E 6BT*

and

*N MCINTOSH  
Department of Child Life and Health,  
University of Edinburgh,  
17 Hatton Place,  
Edinburgh EH9 1NW*