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Research Report

Neonatal morphine enhances nociception and decreases analgesia in young rats

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ABSTRACT

The recognition of the impact of neonatal pain experience on subsequent sensory processing has led to the increased advocacy for the use of opioids for pain relief in infants. However, following long-term opioid exposure in intensive care units more than 48% of infants exhibited behaviors indicative of opioid abstinence syndrome, a developmentally equivalent set of behaviors to opioid withdrawal as seen in adults. Little is known about the long-term influence of repeated neonatal morphine exposure on nociception and analgesia. To investigate this, we examined mechanical and thermal nociception on postnatal days 11, 13, 15, 19, 24, 29, 39 and 48 following subcutaneous administration of morphine (3 mg/kg) once daily on postnatal days 1–9. The cumulative morphine dose-response was assessed on postnatal days 20 and 49, and stress-induced analgesia was assessed on postnatal days 29 and 49. Both basal mechanical and thermal nociception in neonatal, morphine-exposed rats were significantly lower than those in saline-exposed, handled-control rats and naive rats until P29. A rightward-shift of cumulative dose-response curves for morphine analgesia upon chronic neonatal morphine was observed both on P20 and P49. The swim stress-induced analgesia was significantly decreased in neonatal morphine-exposed rats on P29, but not on P49. These data indicate that morphine exposure equivalent to the third trimester of gestation produced prolonged pain hypersensitivity, decreased morphine antinociception, and decreased stress-induced analgesia. The present study illustrates the need to examine the long-term influence of prenatal morphine exposure on pain and analgesia in the human pediatric population.

1. Introduction

Twenty years ago, pain was not mentioned in the textbooks of pediatric medicine due to several misconceptions, including the mistaken notions that: 1) infants and children did not feel pain, 2) they would not remember the pain, 3) pain built character, and 4) opiates were too dangerous to use. The reality is that infants and children not only experience pain but may in fact have decreased pain thresholds and increased physiological responses to both noxious and innocuous stimuli as compared to older children and adults (Craig et al., 1993; Grunau et al., 1994; Johnston et al., 1996, 1995). Of even greater consequence is the recognition that early painful experiences may have long-term effects on later pain behaviors (Johnston et al., 1996; Fitzgerald et al., 1989; Grunau et al., 2006, 1994; Oberlander et al., 2000; Peters et al., 2005; Ruda et al., 2000; Saigal et al., 1994; Taddio and Katz, 2005; Taddio et al., 1997). The abnormal behavioral and physiological responses of early pain-exposed infants to future

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Table 1 – Body weights (g) across the experiment did not change across treatment groups prior to weaning

Postnatal day	Morphine	Saline	Handled	Naive
P1	6.5±0.1	6.6±0.1	7.0±0.3	+
P2	7.2±0.1	7.7±0.2	7.3±0.3	+
P3	8.4±0.2	8.5±0.2	8.3±0.4	+
P4	9.8±0.2	10.0±0.2	9.7±0.5	+
P5	11.1±0.2	11.5±0.2	11.3±0.5	+
P6	12.8±0.3	13.3±0.2	13.0±0.6	+
P7	14.9±0.3	15.2±0.3	14.2±0.6	+
P8	16.8±0.3	16.8±0.3	16.1±0.7	+
P9	18.9±0.3	18.8±0.4	17.5±0.8	+
P11	23.8±0.4	22.6±0.5	21.2±0.8	23.1±0.5
P13	28.6±0.5	26.8±0.7	25.0±0.8	28.2±0.5
P15	33.4±0.5	30.7±0.8	29.1±0.8	32.3±0.5
P19	42.3±0.5	40.8±0.9	38.0±1.1	41.2±0.5

+To avoid handling the naive animals weights were not measured at these time points.

noxious stimuli vary depending on the timing of the neonatal insult and the use of anesthesia (Taddio and Katz, 2005). Basic science studies using rodent models of neonatal pain to assess long-term alterations in nociception support the clinical evidence of long-term alterations in pain processing following neonatal pain experience (Alvares et al., 2000; Anand et al., 1999; Lidow et al., 2001; Lidow, 2002; Ruda et al., 2000).

With these monumental changes in perspective on pain during infancy and early childhood there has been increased focus on pediatric pain management. With the recognition of the long-term effects of under-treated pain in infants and children there has been an increase in the use of analgesic agents in this patient population. Opioid analgesics remain the "gold standard" for pain relief in acute pain management in the hospital setting. Currently, human infants and children are routinely treated with opioids for pain relief, especially with chronic opioid exposure for sedation to permit mechanical ventilation in the intensive care units. Unfortunately, more than 48% of infants and children administered therapeutic doses of intravenous opioids in the intensive care units demonstrate symptoms of opiate withdrawal (Arnold et al., 1990; Franck and Vilardi, 1995; Franck et al., 1998; French and Nocera, 1994; Norton, 1988).

In the adult population opioids can produce a paradoxical hyperalgesia (Angst and Clark, 2006) that manifests both during withdrawal (Angst et al., 2003) as well as while undergoing chronic therapy (Chu et al., 2006). A prolonged decrease in pain threshold is reported in adult methadone maintenance patients compared to non-addict siblings and interestingly the decrease in pain threshold also remains lower in ex-opioid addicts as compared to a control population that does not have a substance abuse disorder (Compton, 1994; Compton et al., 2000, 2001; Doverty et al., 2001a,b; Ho and Dole, 1979). Whether exposure to opioids in pre-term infants causes long-term alterations in pain thresholds is currently unknown.

Our laboratory has recently shown that acute morphine administration in young rats produces spontaneous or precipitated withdrawal-associated pain hypersensitivity (Sweitzer et al., 2004a,b; Zissen et al., 2007) that is equivalent to that observed in adults (Bederson et al., 1990; Kim et al., 1990). Furthermore, this exposure can have lasting effects on inflammatory pain experienced later in childhood (Zissen et al., 2006). Dramatic changes in pain processing and opioid systems (Fitzgerald and Jennings, 1999) in neonates coupled with the repeated morphine exposure in pre-term infants in the neonatal intensive care unit, make it necessary to investigate the possible long-term influence of chronic morphine exposure in neonates on nociceptive pathways and analgesia.

The maturation of nociceptive circuitry is a dynamic and activity-dependent process that begins during prenatal development and extends into postnatal development in both rats and humans (Fitzgerald and Jennings, 1999). A newborn rat is less mature at birth compared to a human and thus, the first postnatal week in a rat is approximately equivalent to the third trimester in a human fetus or a pre-term infant in the neonatal intensive care unit. Furthermore the second to third postnatal week in a rat is approximately equivalent to the first few years of life in a human infant/child. The present study investigated

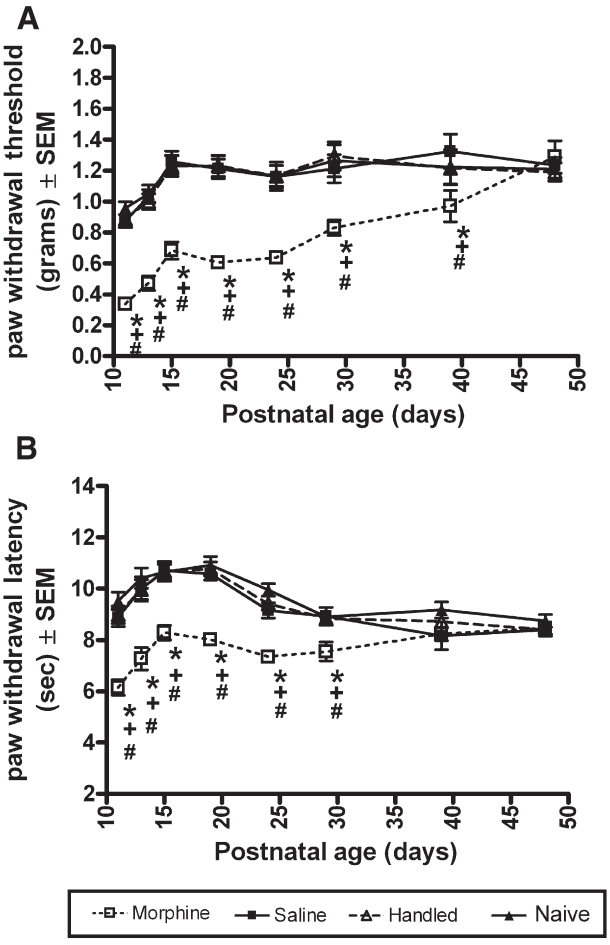

Fig. 1 – The time courses of changes in mechanical and thermal nociception in neonatal morphine-exposed rats. Mechanical allodynia (A) and thermal hyperalgesia (B) were present into early adolescence (postnatal day 30) following third trimester-equivalent morphine exposure and compared to saline and handled-controls or naive rats. Data are expressed as mean ± SEM. *P<0.05 significance compared to saline control rats; +P<0.05 significance compared to handled-control rats; #P<0.05 significance compared to naive rats.