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REVIEW

NEONATAL PAIN AND REDUCED MATERNAL CARE: EARLY-LIFE STRESSORS INTERACTING TO IMPACT BRAIN AND BEHAVIORAL DEVELOPMENT

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Abstract—Advances in neonatal intensive care units (NICUs) have drastically increased the survival chances of preterm infants. However, preterm infants are still exposed to a wide range of stressors during their stay in the NICU, which include painful procedures and reduced maternal contact. The activation of the hypothalamic–pituitary–adrenal (HPA) axis, in response to these stressors during this critical period of brain development, has been associated with many acute and long-term adverse biobehavioral outcomes. Recent research has shown that Kangaroo care, a non-pharmacological analgesic based on increased skin-to-skin contact between the neonate and the mother, negates the adverse outcomes associated with neonatal pain and reduced maternal care, however the biological mechanism remains widely unknown. This review summarizes findings from both human and rodent literature investigating neonatal pain and reduced maternal care independently, primarily focusing on the role of the HPA axis and biobehavioral outcomes. The physiological and positive outcomes of Kangaroo care will also be discussed in terms of how dampening of the HPA axis response to neonatal pain and increased maternal care may account for positive outcomes associated with Kangaroo care.

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Key words: NICU painful procedures, maternal separation, Kangaroo care, hypothalamic–pituitary–adrenal axis (HPA), early-life adversity, preterm infants.

Contents

INTRODUCTION

Preterm births account for 11.1% of all live births worldwide (Blencowe et al., 2012) and the numbers are still increasing (by 1% from 1990 to 2010) even in developed countries such as the United States. Survival rates on the other hand have improved dramatically so that even extremely early preterm infants (i.e. 23 weeks) now have a 23–33% chance of survival (Rysavy et al., 2015). However, being born very premature often results in cognitive and behavioral deficits and there is a dearth of knowledge about what contributes to the long-term biobehavioral outcomes following preterm birth. One consistent and widely documented finding relates to altered brain maturation in preterm infants which has been observed at multiple developmental stages including infancy (Woodward et al., 2006), childhood (Peterson et al., 2000), and young adulthood (Nosarti et al., 2014). These alterations in brain maturation may manifest as cognitive impairments (Stewart et al., 1999; Bhutta et al., 2001; Marlow et al., 2005; Marlow et al., 2007; Fraello et al., 2011) and altered internalizing behaviors (anxiety/depression; Spittle et al., 2009) seen in preterm infants later in life. Further, preterm birth has been associated with a higher risk of psychiatric disorders such as non-affective psychosis, depressive disorder, attention deficit hyperactivity disorder, autism spectrum disorder, and alterations to the hypothalamic–pituitary–adrenal (HPA) axis (Grunau et al., 2007; Johnson et al., 2010; Nosarti et al., 2012).

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Abbreviations: ACTH, adrencorticotropic hormone; CGA, corrected gestational age; CRF, corticotrophin releasing factor; CRFR, corticotrophin releasing factor receptors; EEG, electroencephalogram; GR, glucocorticoid receptor; HPA, hypothalamic–pituitary–adrenal axis; NICUs, neonatal intensive care units; PTSD, post-traumatic stress disorder; PVN, paraventricular nucleus.

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Although previous research links preterm birth itself to various negative biological and behavioral outcomes (Aylward, 2005), it has been suggested that the impaired brain maturation and altered behavioral outcomes may be – at least partly – a product of environmental stressors such as pain exposure during early-life (Anand and Hickey, 1987; Anand and Scalzo, 2000; Grunau et al., 2006). Neonates are exposed to a variety of stressors while in the neonatal intensive care unit (NICU) including neonatal pain, decreased maternal care, altered auditory and light stimulation, mechanical ventilation, nursing procedures, and medical treatments. Further, preterm infants have a high risk of infections and other medical complications (Platt, 2014). It is conceivable that the multitude of stressors these infants are exposed to contributes to their biobehavioral development. In line with this, recent research has shown that increasing the number of stressors (light, sound, handling, or pain) present at any given time typically produces an increase in heart rate, respiratory rate, oxygen saturation, and facial grimacing (Peng et al., 2009), all of which are symptoms of neonatal distress. Further, Holsti et al. (2007) demonstrated that behavioral responses to pain are heightened in preterm neonates after clustered routine nursing interventions. More recently, several studies provided evidence for a direct link between the exposure to painful procedures and altered brain and behavioral development (Brummelte et al., 2012; Ranger et al., 2013).

Preterm infants usually experience less maternal care while they are in the NICU or special care nursery than they would at home. Interestingly, previous animal studies have shown a potential modulatory role of maternal care on the stress of neonatal pain (Blass et al., 1995). Further, both neonatal pain and reduced maternal care promote HPA axis activation (Kuhn et al., 1990; Victoria et al., 2014) which may be exacerbated when exposed to both stressors simultaneously. One way to increase maternal care in the NICU setting is through the use of Kangaroo care (increased skin-to-skin contact between the neonate and mother) which is a nonpharmalogical analgesic for premature infants (Johnston et al., 2003) and has been linked to positive outcomes which range from typical brain development to improved cognitive functioning (Scher et al., 2009; Feldman et al., 2014). Due to the positive outcomes, the use of Kangaroo care has increased in the United States (Engler et al., 2002), however, the question as to how Kangaroo care produces positive outcomes remains widely unknown. Better understanding of the biological mechanism by which Kangaroo care produces positive biobehavioral outcomes may help to implement Kangaroo care as a standard care practice in more hospitals around the globe and may help further optimize the preterm environment.

This review will provide a comprehensive overview of both human and animal literature investigating the independent biobehavioral impacts of neonatal pain and reduced maternal care with a specific focus on the role of the HPA axis. Moreover, we will discuss the hypothesis that increased maternal care may dampen the HPA axis response to neonatal pain and thus account for positive outcomes associated with Kangaroo care. Finally, this review will discuss future directions in the field of neonatal pain and reduced maternal care and how we can improve the conditions and thus improve developmental outcomes for preterm infants.

NEONATAL PAIN

Development of pain pathways and pain exposure

The biological system for the perception of pain in mammals is very complex and relies on input from both the peripheral and central nervous system (for review see Millan, 1999). From the spinal cord perception of pain is carried in an ascending manner to many supraspinal regions including, but not limited to, the various nuclei of the thalamus and hypothalamus, sensory cortex, amygdala, insula, and various sections of the cingulate and prefrontal cortices (Brooks and Tracey, 2005). It is beyond the scope of this paper to review the full complexity of the pain system, but it is clear that pain is a multidimensional and multisensory modality and that it relies on many intact systems and components to produce its affective and sensory experience.

It was once widely believed that neonates were unable to perceive pain due to an underdeveloped neural system and as a consequence some surgeries were performed on neonates without analgesia (Rodkey and Pillai Riddell, 2013). Fortunately, this belief has since been discredited through neuroanatomical and behavioral studies providing evidence for early development of pain pathways (Anand and Hickey, 1987). In rodents, the afferent neurons responsible for relaying the detection of noxious stimuli innervate the dorsal horn as early as embryonic day 14 (Jackman and Fitzgerald, 2000). In humans, the afferents from the dorsal horn that project to the spinal cord develop between the 8th and 19th week of gestation (Konstantinidou et al., 1995). Even though peripheral systems may be in place to perceive noxious stimuli at a very early stage, it has been argued that pain cannot be fully perceived until afferent projections from the thalamus have reached their destined targets. Upon the departure of the subplate zone, neurons innervate their target and allow the connections from the thalamus to be complete as early as 28 weeks gestation (Kostovic and Goldman-Rakic, 1983), though painful procedures can elicit activation of the somatosensory cortex as early as 25 weeks gestation (Bartocci et al., 2006; Slater et al., 2006). Behavioral findings further support the foregoing neuroanatomical evidence of pain perception in neonates, as even very young preterm infants show heightened levels of facial grimacing, crying, and full body reflexive withdrawal in response to a painful stimulus (Stevens et al., 1994; Johnston et al., 1995; Abdulkader et al., 2008). In summary, these findings demonstrate that preterm infants have the proper neuroanatomical systems in place to perceive pain as well as the behavioral tools to respond to painful stimuli.

Although it has been clearly demonstrated that preterm infants are capable of perceiving pain, they are still subjected to many painful medical procedures while

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