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Brain development in rodents and humans: Identifying benchmarks of maturation and vulnerability to injury across species

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ABSTRACT

Hypoxic-ischemic and traumatic brain injuries are leading causes of long-term mortality and disability in infants and children. Although several preclinical models using rodents of different ages have been developed, species differences in the timing of key brain maturation events can render comparisons of vulnerability and regenerative capacities difficult to interpret. Traditional models of developmental brain injury have utilized rodents at postnatal day 7–10 as being roughly equivalent to a term human infant, based historically on the measurement of post-mortem brain weights during the 1970s. Here we will examine fundamental brain development processes that occur in both rodents and humans, to delineate a comparable time course of postnatal brain development across species. We consider the timing of neurogenesis, synaptogenesis, gliogenesis, oligodendrocyte maturation and age-dependent behaviors that coincide with developmentally regulated molecular and biochemical changes. In general, while the time scale is considerably different, the sequence of key events in brain maturation is largely consistent between humans and rodents. Further, there are distinct parallels in regional vulnerability as well as functional consequences in response to brain injuries. With a focus on developmental hypoxic-ischemic encephalopathy and traumatic brain injury, this review offers guidelines for researchers when considering the most appropriate rodent age for the developmental stage or process of interest to approximate human brain development.

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Abbreviations: CNS, Central nervous system; GAB, Agamma-Aminobutyric acid; GCL, granule cell layer; Gd, gestation day; HI, hypoxia-ischemia/hypoxic-ischemic; HIE, hypoxic-ischemic encephalopathy; IL, interleukin; MRI, magnetic resonance imaging; NMDA, *N*-methyl-D-aspartate; OL, oligodendrocyte; pnd, postnatal day; pre-OL, pre-oligodendrocyte; SGZ, subgranular zone; SVZ, subventricular zone; TBI, traumatic brain injury; 5-HT, 5-hydroxytryptamine.

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1. Introduction

Rodent models of ischemic and traumatic brain injury are frequently used in research laboratories, both to investigate the underlying mechanisms of injury vulnerability and evaluate potential therapeutic approaches. Perinatal hypoxic-ischemic encephalopathy (HI or HIE) accounts for 25% of developmental disabilities in children, occurring in 1% of all full-term births (Shevell et al., 2000). Perinatal asphyxia-induced brain injury is one of the most common causes of morbidity and mortality in term and preterm neonates, accounting for 23% of neonatal deaths globally (Lawn et al., 2005). Neonatal stroke, a cerebrovascular event which occurs between 28 weeks gestation and one postnatal month of age, may be either hemorrhagic or HI in origin and has been associated with consequences including cerebral palsy and behavioral abnormalities (Lee et al., 2005; Lynch, 2009). Traumatic brain injury (TBI) is a leading cause of long-term neurocognitive and psychosocial deficits in infants and young children worldwide (Mazzola and Adelson, 2002; Selassie et al., 2008), with an estimated 475,000 cases of TBI in 0–14 year old children each year in the US (Langlois et al., 2005). Rates are highest in children under 4 years of age, and TBI sustained during early childhood typically results in poorer outcomes and longer recovery times compared to children who sustain injury in later childhood or adolescence (Catroppa et al., 2008; Duval et al., 2008). Regardless of the injury type or mechanism, traumatic and ischemic injuries share many common pathological mechanisms (Kochanek, 1993), and it is increasingly evident that the developing brain responds differently to injury compared to the adult brain (Babikian et al., 2010; Blomgren et al., 2007; Claus et al., 2010; Giza et al., 2007; Hu et al., 2000; Potts et al., 2006; Qiu et al., 2007; Zhu et al., 2009, 2005). It is thus crucial that we gain a better understanding of the unique properties intrinsic to the developing brain and its response to insult (Giza et al., 2009). The number of paradigms to model the injured immature brain is growing, using different animals of varying ages (Balduini et al., 2000; Bittigau et al., 2003; Claus et al., 2010; Ikonomidou and Kaindl, 2011; Tai et al., 2009; Zhu et al., 2005). Yet questions of comparability across species continue to create controversy. Which ages in rodents best correspond to the premature, newborn at term, infant, child and adolescent human? Which aspects of brain development are most essential to equate to humans when using an animal model? Keeping in mind that no given model is likely to fully mimic the human disease or condition, we suggest that it is most important to accurately define and correlate general mechanisms of injury and neuroprotection, which are often dependent on the maturation stage of the nervous system (Hagberg et al., 2002a).

Here, we will review key events that accompany brain development in both rodents and humans to identify temporal 'benchmarks' where there is heightened vulnerability to injury during infancy, childhood and adolescence. Developmental changes in neuroanatomy, cell proliferation, synaptogenesis and myelination will be discussed, as well as differential immune responses seen at different ages. Lastly, the emergence of age-dependent behaviors in rodents and humans will be considered in relation to ongoing developmentally regulated molecular and anatomical changes. The impact of TBI or HIE at different developmental processes will be highlighted throughout, to emphasize the complex interplay between injury mechanisms superimposed upon maturation-related changes in brain structure and function.

2. Gross neuroanatomy

The first major event of central nervous system (CNS) development in all vertebrates is the formation of a specialized fold of ectodermal tissue called the neural tube, from which the spinal cord and brain subsequently differentiate. Neural tube formation occurs approximately mid-gestation in rodents, on gestational day (gd) 10.5–11 and 9–9.5 in rats and mice, respectively, with birth typically occurring on gd 20–21. In humans, this event occurs earlier during prenatal development, between gd 24 and 28 (3–4 weeks) out of a gestation period of 266–280 days (40 weeks) (DeSesso et al., 1999; Rice and Barone, 2000). The key stages of cortical development during fetal brain formation are remarkably conserved between mammalian species and have been extensively described elsewhere (Clancy et al., 2007; Finlay and Darlington, 1995; Molnár and Clowry, 2012; Monk et al., 2001). This has allowed for the implementation of an online database for translating early neurodevelopmental milestones between species. A collaboration between the University of Central Arkansas and Cornell University has resulted in a statistical-based algorithm which integrates data from 10 different mammalian species, across key events up to post-conception day 156 in humans (www.translatingtime.org) (Clancy et al., 2007). These collaborators concede the difficulty of extending such a model to encapsulate peri- and postnatal periods, when a maturing brain is more profoundly affected by activity and environmental influences.

In the postnatal brain, species' differences in brain development were historically assessed by the measurement of post-mortem tissue weights. Dobbing and Sands generated much of the groundwork in this area of comparative neuroanatomy, by characterizing the brain growth trajectories across seven mammalian species based on weight changes over time. In particular, they examined the timing of the brain growth spurt, defined as the total brain weight gain as a percentage of its adult weight, found to peak in humans around birth and postnatal day (pnd) 7 in rats (Dobbing and Sands, 1979). This likely founded the widespread 'rule of thumb' usage of 7-day-old rat pups to investigate perinatal scenarios (Vannucci, 1990; Yager and Ashwal, 2009). The rat cortex reaches approximately 90% of its adult weight by pnd 20, the typical age of weaning in rodents. In humans, brain weight reaches a similar plateau by 2–3 years of age (Dekaban et al., 1987; Dobbing and Sands, 1973, 1979). Thus, based on brain weights alone, pnd 20 in rats appears to correspond to a 2–3 year old human child (Table 1). Importantly, however, these early studies do not account for the considerable heterogeneity between different brain regions, which likely mature at different rates.

Advancements in non-invasive imaging techniques during the 1990s stimulated a period of renewed interest in developmental brain growth in humans, with serial magnetic resonance imaging (MRI) allowing for the discrimination of gray and white matter and cortical thickness (Lenroot et al., 2007). By MRI, brain volume in typically developing children reaches 90–95% of its adult size by the age of 6, slightly later than earlier estimates from post-mortem studies, before peaking at 10.5 years in females and 14.5 years in males (Bansal et al., 2008; Giedd et al., 1999; Lenroot and Giedd, 2006) (Fig. 1). Of note, dramatic changes are evident in both cortical and subcortical structures during childhood and adolescence. Using conventional MRI sequences, the intensity of gray and white matter during the first 6 months of life in humans are reversed from the adult (i.e. gray matter appears lighter than white matter). Between 6 and 12 months, a regionally specific transition period is evident during which gray and white matter are poorly differentiated, consistent with a decrease in water content and the accumulation of myelin (Inder and Huppi, 2000; Paus et al., 2001). White matter subsequently increases linearly across most brain regions with increasing age, beginning towards the end of the second trimester and continuing well into the third decade of life (Giedd et al., 1999). Changes in gray matter volumes tend to be region-specific, and follow an inverted U-shaped trajectory during