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Hepatic acute phase response protects the brain from focal inflammation during postnatal window of susceptibility

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ABSTRACT

Perinatal inflammation is known to contribute to neurodevelopmental diseases. Animal models of perinatal inflammation have revealed that the inflammatory response within the brain is age dependent, but the regulators of this variation remain unclear. In the adult, the peripheral acute phase response (APR) is known to be pivotal in the downstream recruitment of leukocytes to the injured brain. The relationship between perinatal brain injury and the APR has not been established. Here, we generated focal inflammation in the brain using interleukin (IL)-1β at postnatal day (P)7, P14, P21 and P56 and studied both the central nervous system (CNS) and hepatic inflammatory responses at 4 h. We found that there is a significant window of susceptibility in mice at P14, when compared to mice at P7, P21 and P56. This was reflected in increased neutrophil recruitment to the CNS, as well as an increase in blood–brain barrier permeability. To investigate phenomena underlying this window of susceptibility, we performed a dose response of IL-1β. Whilst induction of endogenous IL-1β or intercellular adhesion molecule (ICAM)-1 in the brain and induction of a hepatic APR were dose dependent, the recruitment of neutrophils and associated blood–brain barrier breakdown was inversely proportional. Furthermore, in contrast to adult animals, an additional peripheral challenge (intravenous IL-1β) reduced the degree of CNS inflammation, rather than exacerbating it. Together these results suggest a unique window of susceptibility to CNS injury, meaning that suppressing systemic inflammation after brain injury may exacerbate the damage caused, in an age-dependent manner.

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1. Introduction

Neuroinflammation is implicated in the aetiology of neurodevelopmental disorders, such as autism, schizophrenia (Bayer et al., 1999; Bloomfield et al., 2016; Estes and McAllister, 2015; Fillman et al., 2013; Trépanier et al., 2016; Vargas et al., 2005) and cerebral palsy (Kadhim et al., 2003, 2001; Mallard et al., 2014). The impact of inflammation on development appears to be highly dependent on the timing of the challenge; for instance, autism and schizophrenia have been associated with infection during the first and second trimester, while vulnerability to cerebral palsy was highest in the last trimester and early postnatal period (Atladóttir et al., 2010; Brown et al., 2004; Dubowitz et al., 1985; Mednick et al., 1988).

Inflammatory challenges in rodents at different time points during development have revealed that there are striking differences in the nature of the cellular and molecular responses (Lawson and Perry, 1995; Meyer et al., 2006; Straley et al., 2017). For example, a window of susceptibility exists in rats at three-weeks postpartum, when the generation of a focal inflammatory lesion in the brain results in increased leukocyte recruitment and blood–brain barrier breakdown, which is not observed either

Abbreviations: APR, acute phase response; CNS, central nervous system; CXCL, C-X-C motif ligand; IL, interleukin; ICAM, intercellular adhesion molecule; P, postnatal day; LPS, lipopolysaccharide; PBS, phosphate-buffered saline; rrIL-1β, rat recombinant IL-1β; RT-qPCR, Real-Time polymerase chain reaction; SEM, standard error of the mean; TNF, tumour necrosis factor.

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before or after this window (Anthony et al., 1997). Peripheral immune activation by the intraperitoneal injection of lipopolysaccharide (LPS) has also been shown to transiently increased blood–brain barrier permeability in the periventricular white matter tracts during the first postnatal week in rats (Stolp et al., 2005) and an intraperitoneal injection of LPS followed by hypoxia–ischemia was shown to increase blood–brain barrier permeability at postnatal day (P)12 but not at P1 in Lewis rats (Brochu et al., 2011). Both studies from Anthony et al. (1997) and Brochu et al. (2011) have correlated blood–brain barrier permeability with the recruitment of neutrophils to the brain. These variations in the inflammatory response during development may alter cortical development and have a lasting impact on behaviour (Stolp et al., 2011a,b).

In adults, focal cerebral inflammation (Campbell et al., 2005, 2003; Wilcockson et al., 2002), traumatic brain injury (Villapol et al., 2015) and cerebral ischemia (Chapman et al., 2009) in rodents have been shown to induce the hepatic acute phase response (APR) characterized by the expression of cytokines and chemokines, other acute phase proteins such as serum amyloid A, and the recruitment of neutrophils and macrophages. Campbell et al. (2003) observed that an intracerebral injection of interleukin (IL)-1β induced the production and release of C-X-C motif ligand (CXCL)-1 by the liver and the recruitment of neutrophils to the liver, blood and brain in a dose-dependent manner. The hepatic APR functions to eliminate the inflammatory stimuli, attenuate local inflammation, and promote tissue repair and regeneration (Anthony et al., 2012; Anthony and Couch, 2014). However, by recruiting and priming leukocytes to the site of injury in the central nervous system (CNS), the APR may also contribute to further damage in the brain. Systemic inflammation has been shown to exacerbate focal neuroinflammatory injury in the adult. A number of rodent and human studies have demonstrated a positive correlation between the magnitude of the APR and brain injury (Acalovschi et al., 2003; Campbell et al., 2003; Di Napoli et al., 2005; Smith et al., 2006, 2004; Vila et al., 2000; Villapol, 2016).

In the perinatal period, an altered hepatic APR has also been reported following hypoxic-ischemic encephalopathy in rats, which was characterized by upregulation of CXCL-1 and downregulation of tumour necrosis factor (TNF), IL-1β and CCL-2 (Bonestroo et al., 2013). However, the nature of this response, and how it affects the evolution of the central injury, is still unclear. It is likely that, as in adult, the hepatic APR may impact the magnitude of the CNS immune response and subsequent secondary injury.

In this study, we use a well-established model of focal intracerebral inflammation to study the role of the hepatic APR in modulating the brain response to acute inflammation during postnatal development. The intrastriatal injection of IL-1β generates a reproducible focal inflammatory lesion which is accompanied by de novo production of cytokines, the activation of microglia and local endothelial cells in the absence of acute neuronal cell death (Campbell et al., 2007a,b; Docagne et al., 2005; van Kasteren et al., 2009). The local cellular response to the inflammatory challenge is conspicuous from 4 h to 7 days post injection (Docagne et al., 2005). Here we show that susceptibility of the brain to focal inflammation varies with age, and that contrary to expectations, the CNS response is inversely proportional to the APR during the window of susceptibility.

2. Materials and methods

2.1. Animals

C57Bl/6 mice were used at postnatal day (P)7, P14, P21 and P56. These ages were selected based on a previous publication in rats (Anthony et al., 1997), and on preliminary data from our own lab in mice, showing a mid-to-late postnatal window of susceptibility to an inflammatory challenge that is likely to be related to the increased susceptibility of children to CNS infections and injury (Catroppa et al., 2008; Duval et al., 2008; Semple et al., 2013). Mice were obtained from Harlan, UK, and acclimatised for at least 3 days to the local environment prior to experimentation. Animals were housed in specific pathogen-free facilities under a standard light/-dark cycle with food and water ad libitum. All animal procedures were conducted in accordance with the U.K. Animals (Scientific Procedures) Act, 1986 and associated guidelines, EU Directive 2010/63/EU for animal experiments (PPL: 30/3076). Both male and female pups were used in these experiments; no effect of sex was identified in any response measured. Litters were split between experimental groups to limit any effect of maternal care on the experiments. The number of animals used in each group studied can be found in figure legends.

2.2. Administration of IL-1β

Animals were anaesthetised with 2–3% isoflurane in oxygen. Stereotaxic surgery was performed under an operating microscope, as previously described (Couch et al., 2014). The top of the head was shaved and positioned in a stereotaxic frame. The skull was exposed and a small hole made with dental drill burr (Bregma: A nterior/Posterior + 0.5 mm; Medial/Lateral + 1 mm (P7, P14), 1.5 mm (P21) or 1.8 mm (P56); Dorsal/Ventral – 1.7 mm (P7) or 2 mm (P14, P21, P56). Rat recombinant IL-1β (rrIL-1β, 501-RL/CF; 2 ng/μl, 20 ng/μl or 200 ng/μl; R&D Systems, UK) or vehicle (0.9% saline) were injected into the left striatum with finely-drawn glass microcapillary needle (0.5 μl over a period of 5 min), and the wound was closed using surgical clips. All coordinates were defined using dye injections in preliminary experiments. In a cohort of mice at P14, saline or 100 ng of rrIL-1β (50 μl) was injected into the tail vein immediately after the intracerebral injection outlined above. This dose of IL-1β was chosen based on previous results showing that 100 ng of IL-1β induces the hepatic expression of factor nuclear kappa B (NFkB), which regulates neutrophil recruitment to the injured brain, at a similar level to the focal intracerebral injection of IL-1β (Campbell et al., 2008). Animals recovered in a heated chamber before being returned to their cage.

2.3. Tissue preparation

Two or four hours following intracerebral or intravenous injection of rrIL-1β or saline, mice were anaesthetized with pentobarbital (20% w/v pentobarbital sodium, i.p.; J M Loveridge Ltd, UK) and then transcardially perfused with cold 0.9% saline with heparin (Sigma, UK). Liver and striatum were frozen on dry ice for mRNA extraction. The striatum was dissected into ipsilateral (injected) and contralateral side from saline and IL-1β injected animals, and the contralateral (right) side from naïve animals. Alternately, mice were transcardially perfused fixed with 4% paraformaldehyde (in 0.1 M phosphate buffer, pH 7.4) after 0.9% saline with heparin (Sigma, UK). Brain and liver were collected and immersed into 4% paraformaldehyde at 4 °C for 24 h, before cryoprotection in 30% sucrose (4 °C) and subsequently embedded in O.C.T. compound (CellPath, UK). Ten-micrometer-thick sections were cut on a cryostat Leica CM1850 (Leica Microsystems, UK) and mounted on gelatin-coated slides in a serial manner. Brain sections were collected for the full extent of the injection site and lesion, from approximately Bregma + 1.10 to – 0.10, based on The Mouse Brain in Stereotaxic Coordinates (Paxinos and Franklin).

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