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Review

Understanding disease processes in multiple sclerosis through magnetic resonance imaging studies in animal models

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ABSTRACT

There are exciting new advances in multiple sclerosis (MS) resulting in a growing understanding of both the complexity of the disorder and the relative involvement of grey matter, white matter and inflammation. Increasing need for preclinical imaging is anticipated, as animal models provide insights into the pathophysiology of the disease. Magnetic resonance (MR) is the key imaging tool used to diagnose and to monitor disease progression in MS, and thus will be a cornerstone for future research. Although gadolinium-enhancing and T_2 lesions on MRI have been useful for detecting MS pathology, they are not correlative of disability. Therefore, new MRI methods are needed. Such methods require validation in animal models. The increasing necessity for MRI of animal models makes it critical and timely to understand what research has been conducted in this area and what potential there is for use of MRI in preclinical models of MS. Here, we provide a review of MRI and magnetic resonance spectroscopy (MRS) studies that have been carried out in animal models of MS that focus on pathology. We compare the MRI phenotypes of animals and patients and provide advice on how best to use animal MR studies to increase our understanding of the linkages between MR and pathology in patients. This review describes how MRI studies of animal models have been, and will continue to be, used in the ongoing effort to understand MS.

1. Introduction

Multiple sclerosis (MS) is an inflammatory, demyelinating and degenerative condition of the central nervous system (CNS) for which the cause is unknown. Animal models of MS have greatly enhanced knowledge of the pathophysiology of the disease. Each of these animal models provides different potential routes to investigate MS disease processes. The experimental autoimmune encephalomyelitis (EAE) model provides the opportunity to study inflammation, demyelination and axonal loss initiated by an autoimmune response to central nervous system (CNS) components. Viral models, particularly those induced by Theiler's murine encephalomyelitis virus (TMEV), enable examination of an immune response to a viral infection leading to demyelination. Demyelinating models caused by toxins such as lysolecithin, cuprizone and ethidium bromide afford the opportunity to investigate a primary demyelinating insult.

Magnetic resonance imaging (MRI) plays an integral role in the diagnosis of MS, for tracking the disease course, and for determining the effectiveness of treatments (for a review, refer to Filippi and Rocca, 2011). New MRI methods are continually being developed to provide more information about MS disease processes with the goal of improving the correlation of MRI with clinical disability. Ideally, knowledge gained from MRI studies in animal models can be translated to human studies to improve the interpretation of MRI and to inform human studies on elements of disease.

Here, we review MRI and magnetic resonance spectroscopy (MRS) studies of animal models of MS specifically with respect to investigating pathology. We relate these to what has been found in MS patients. We previously reviewed the use of MRI studies of animal models of MS for testing drugs in MS (Nathoo et al., 2014). We also discuss how MRI can be applied to answer questions about the pathophysiology of MS using animal models of MS. Such studies at the preclinical stage have the potential to direct subsequent application of MRI in the human MS population.

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2. MRI studies in animal models of MS

2.1. Experimental autoimmune encephalomyelitis (EAE)

EAE is a model of chronic inflammation and is the animal model used most often to investigate MS. Many variants of the EAE model exist that can display monophasic, relapsing–remitting, chronic-progressive or chronic-relapsing disease courses depending on the animal strain and immunogen used. Taken together, the diverse types of EAE models present the spectrum of clinical phenotypes observed in MS (Kipp et al., 2012). EAE immunization uses components of the CNS which stimulate the immune system via antigen presentation and autoimmunity. The antigen may be from CNS homogenate or purified myelin peptides, such as myelin basic protein (MBP), myelin oligodendrocyte glycoprotein (MOG), or proteolipid protein (PLP). This results in an autoimmune condition which targets myelin. EAE has been induced and examined across species with earlier studies focusing on non-human primates. Rodent models, particularly those using mice, are now more commonly used due to the affordability and availability of genetically modified murine strains (Ransohoff, 2012).

MS and EAE share several characteristics, including the destruction of myelin sheaths and axonal degeneration (Steinman and Zamvil, 2005). In addition, numerous CNS lesions are present which are distributed in space and time (Adams and Kubik, 1952; Baxter, 2007). MS and several variant models of EAE have evidence supporting a genetic susceptibility influenced by major histocompatibility complex class II haplotype (Steinman and Zamvil, 2005). Furthermore, CD4+ and CD8+ T-cells can be seen in lesions in both conditions, some of which are reactive to myelin proteins (Steinman and Zamvil, 2005). Studies have demonstrated that at the molecular level, the process of leukocyte migration into the CNS is similar in EAE to that in MS (Agrawal et al., 2011). For example, activated leukocytes roll and adhere onto endothelial cells via adhesion molecules, and then ultimately cross the glia limitans to enter the CNS parenchyma (Agrawal et al., 2006).

The vast majority of MRI studies with animal models of MS have used the EAE model. Importantly, the EAE model shows the same clinico-radiological paradox seen in MS, where MRI lesion load does not always correspond to the level of clinical disability (Wuerfel et al., 2007).

2.1.1. EAE: imaging non-specific pathological changes

Key pathological processes in MS including inflammation, demyelination, axonal loss and oedema have been assessed using T_2-weighted imaging, where areas of injury appear hyperintense. Although T_2 can identify each of these processes, it cannot differentiate between them, which has made T_2-weighted MRI a method to characterize cumulative damage to the CNS, but not to identify the individual processes responsible for the damage.

In EAE models produced in rodents and primates, lesions have been detected using T_2-weighted MRI, which have been shown to correspond to inflammation, demyelination and axonal loss (DeBoy et al., 2007; Hart et al., 1998; Stewart et al., 1991). These hyperintensities on T_2-weighted MRI have frequently been observed in the periventricular white matter (Hart et al., 1998; Boretius et al., 2006; Kuharik et al., 1988; Verhoye et al., 1996), corresponding well with what is observed in MS (Barkhof et al., 1997). Other areas where T_2 hyperintensities have been seen in EAE animals include the corpus callosum (Hart et al., 1998), cerebellum (Waiczies et al., 2012) and cerebral grey matter (Hart et al., 1998), albeit much less frequently than in the periventricular white matter.

In EAE, changes in T_2 have been observed to precede the onset of clinical signs (Stewart et al., 1991; Waiczies et al., 2012; Karlik et al., 1990; O'Brien et al., 1987). In marmosets with EAE, T_2 lesions in the white matter appear to enlarge over time, with stable lesions being present during later stages of lesion evolution (Boretius et al., 2006). T_2 contrast does not appear to normalize, nor does lesion size decrease over the EAE disease course (Boretius et al., 2006). In addition, acute lesions are not distinguishable from older, more chronic lesions on T_2-weighted MRI (Kuharik et al., 1988). Interestingly, the proportion of animals where T_2 lesions are detected varies between studies, where the lowest proportion has been observed in rats (Dousset et al., 1999a) and guinea pigs (O'Brien et al., 1987; Dousset et al., 1992), and the highest observed in primates (Stewart et al., 1991; Hawkins et al., 1990). It is not clear if this discrepancy is attributable to species differences or to the parameters for the MRI sequence used for T_2. Overall, T_2-weighted MRI has shown similar trends in EAE as in MS.

2.1.2. EAE: imaging blood brain barrier (BBB) breakdown

BBB disruption is a cardinal feature of active inflammatory lesions in MS. T_1-weighted MRI with gadolinium (Gd) is a component of the standard imaging protocol for MS to assess lesions with active, ongoing inflammation (Polman et al., 2011). MRI has been used to assess BBB breakdown in EAE models across species. Interestingly, the presence of Gd-enhancing lesions and Gd enhancement in general is variable amongst studies. Gd-enhancing lesions are present in EAE induced in monkeys (Hart et al., 1998; Blezer et al., 2007), dogs (Kuharik et al., 1988), guinea pigs (Cook et al., 2005; Karlik et al., 1993) and mice (Wuerfel et al., 2007; Waiczies et al., 2012; Nessler et al., 2007; Smorodchenko et al., 2007). However, Gd-enhancing lesions are not observed in some rat (Dousset et al., 1999a) and mouse (Schellenberg et al., 2007) EAE studies.

Gd-enhancing lesions have been observed in the lumbar spinal cord (Cook et al., 2005), brainstem (Wuerfel et al., 2007; Smorodchenko et al., 2007), cerebellum (Wuerfel et al., 2007; Smorodchenko et al., 2007), midbrain (Wuerfel et al., 2007) and periventricular areas (Wuerfel et al., 2007; Kuharik et al., 1988; Smorodchenko et al., 2007) (Fig. 1). BBB breakdown has been shown to take place before the presence of clinical signs in EAE mice (Wuerfel et al., 2007). Even in cases where Gd-enhancing lesions were present in EAE animals, not all of the animals showed such lesions. The percentage of EAE animals with Gd-enhancing lesions is variable, ranging from 47% in guinea pigs (Karlik et al., 1993) up to 100% in mice (Smorodchenko et al., 2007). It is likely that in EAE animals, lesions only have a disrupted BBB for a short time, and as standard time points are used for imaging, such BBB disruption may often be missed. This makes it difficult to use enhancing lesions in EAE as a biomarker of disease progression.

An interesting observation that has been made across numerous studies is that Gd enhancement occurs in areas other than in lesions (shown with histology or T_2-weighted MRI), including in white matter areas away from lesions (Boretius et al., 2006), in the brain parenchyma (Karlik et al., 1993), near the third ventricle (Karlik et al., 1993) and in peripheral regions of the lumbar spinal cord (Schellenberg et al., 2007). In the study with Gd enhancement in the peripheral regions of the lumbar spinal cord, histology showed that inflammatory cells appeared in the same areas which had Gd enhancement (Schellenberg et al., 2007); the co-localization of inflammation (as visualized with histology) with areas of Gd enhancement has been shown by others as well (Hawkins et al., 1990).

Although Gd has proven to be useful for detecting loss of BBB integrity in MS, Gd-enhancing MRI is not frequently used in EAE studies because changes with Gd rarely correspond with T_2 lesions. Instead, more sensitive tools have been proposed for assessing BBB breakdown, such as the gadolinium-based contrast agent, gadofluorine M (Gf). In rodents with EAE, Gf has been used to detect cerebral (Bendszus et al., 2008; Wuerfel et al., 2010) and spinal cord (Bendszus et al., 2008) lesions not seen with Gd or with T_2-weighted MRI (Bendszus et al., 2008) (Fig. 2). Gf lesions correspond well with inflammation seen via staining for macrophages/microglia (Bendszus et al., 2008; Wuerfel et al., 2010), especially in cases of severe inflammation (Bendszus et al., 2008). These studies did not comment on