Multiple Sclerosis and Related Disorders (2014) 3, 555–564

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REVIEW

Experimental autoimmune encephalomyelitis is a good model of multiple sclerosis if used wisely

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Received 21 January 2014; received in revised form 1 May 2014; accepted 5 May 2014

KEYWORDS
Animal models;
Experimental autoimmune encephalomyelitis;
Multiple sclerosis;
Therapeutics

Abstract
Although multiple sclerosis is a uniquely human disease, many pathological features can be induced in experimental autoimmune encephalomyelitis (EAE) models following induction of central nervous system-directed autoimmunity. Whilst it is an imperfect set of models, EAE can be used to identify pathogenic mechanisms and therapeutics. However, the failure to translate many treatments from EAE into human benefit has led some to question the validity of the EAE model. Whilst differences in biology between humans and other species may account for this, it is suggested here that the failure to translate may be considerably influenced by human activity. Basic science contributes to failings in aspects of experimental design and over-interpretation of results and lack of transparency and reproducibility of the studies. Importantly issues in trial design by neurologists and other actions of the pharmaceutical industry destine therapeutics to failure and terminate basic science projects. However animal, particularly mechanism-orientated, studies have increasingly identified useful treatments and provided mechanistic ideas on which most hypothesis-led clinical research is based. Without EAE and other animal studies, clinical investigations will continue to be "look-see" exercises, which will most likely provide more misses than hits and will fail the people with MS that they aim to serve.

Abbreviations: EAE, experimental autoimmune encephalomyelitis; MS, multiple sclerosis; PwMS, person with MS

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http://dx.doi.org/10.1016/j.msard.2014.05.002
2211-0348/

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1. Animals models used to give clues about multiple sclerosis as the pathogenesis is not clear

Multiple sclerosis (MS) is the major cause of non-traumatic disability in young adults. Worldwide over 2.5 million people have MS with the highest rate of 1 in 170 women in Orkney, Scotland (Visser et al., 2012), yet the disease is currently ineffectively controlled. Despite some recent success in limiting relapsing-remitting MS (Compston and Coles, 2002, 2008; Marta and Giovannoni, 2012), there are no effective neuroprotective or repair treatments. Furthermore current disease modifying therapies and symptomatic treatments have undesirable, sometimes life-threatening side-effects (Compston and Coles, 2002; Marta and Giovannoni, 2012). These may limit patient compliance and clinical usefulness (Kapoor et al., 2010; Gnanapavan et al., 2013). It is perhaps therefore not surprising that people with MS (PwMS) turn to alternative and unproven treatments (Bowling, 2011), given the failings of the medical profession and the pharmaceutical industry in delivering a cure. Despite extensive research, improvements in imaging techniques and new insights into the pathology there is no universally accepted view of the actual disease mechanisms of MS, particularly in the different phases of the disease. Therefore, it is not surprising that people have turned to animal models to give them clues towards disease mechanisms and therapeutic avenues.

For many years MS was considered to be an autoimmune-mediated, demyelinating disease of the CNS white matter and this has been modelled using chemical, viral and autoimmune experimental systems (van der Star et al., 2012). However, more recently there has been a reawakening to pathological aspects of MS that has emphasised grey matter involvement, and significant axonal and neuronal degeneration (Ferguson et al., 1997; Trapp et al., 1998; Bø et al., 2003), which are the major substrates for accumulating and irreversible disability. The pathological sequence and pathogenic mechanisms of relapsing and progressive MS is still in part conjecture. This makes modelling of the disease difficult although studying different aspects of the disease, as assumed to occur, is possible using different approaches. The mechanisms underlying MS is a changing landscape with concepts d'jour necessitating different approaches. However, to date, only one model reflects the range of the pathological and clinical features of MS and this is experimental autoimmune encephalomyelitis (EAE) in animals (van der Star et al., 2012).

2. EAE is a range of models demonstrating different pathologies relevant to multiple sclerosis

Experimental autoimmune encephalomyelitis is induced following sensitization to CNS myelin, neural or glial cell antigens and includes a range of immune-driven inflammatory conditions (van der Star et al., 2012). These target predominantly the spinal cord as found notably in rodents, to more marked brain involvement as found in non-human primates ('t Hart et al., 2005). EAE models range from non-demyelinating monophasic clinical disease to a secondary progressive neurodegenerative diseases with the varying disease course and pathology depending on the nature of the immunising antigen and the strain and species of animal used (van der Star et al., 2012). Each model has different merits and different levels of similarities with MS. Experimental autoimmune encephalomyelitis can be induced in most mammalian species, including humans. Whilst early examples of experimentally induced neurological disease was observed following vaccination with rabies virus-infected CNS material (Stuart and Krikorian, 1930), human EAE was more recently found when people with Alzheimer's disease were immunised with human beta amyloid protein (Münch and Robinson, 2002). Human EAE is not however MS, which is a uniquely human disease. Therefore, MS may have a uniquely human cause and pathology where aetiological triggers either may drive an "outside-in" (a peripheral trigger that leads to CNS damage as occurs in EAE) or an "inside-out" (an endogenous CNS trigger that recruits the peripheral immune response) disease (Barnett and Prineas, 2004), that may arise secondary to oligodendrocyte stress and demyelination that is central to the pathology of MS (van Noort et al., 2012). Loss of oligodendrocytes is clearly not sufficient to trigger CNS autoimmunity (Locatelli et al., 2012) and probably involves a complex mixture of genetic susceptibility and environmental factors. A central component to the generation of autoimmunity occurs once normal homoeostatic control is lost and a primed autoreactive T cell response is generated. These autoreactive T cells may circulate round the body and once triggered, for example by infection, migrate into tissues such as the CNS disease, where a relapsing neurological disease can be triggered (Goverman et al., 1993). Such a scenario is clearly the pathological basis of EAE, which can be biased towards either a CD4 or CD8 T cell-mediated response. This concept has shaped the view to treatment of MS over many years