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# Sex-dependent effects of chronic restraint stress during early Theiler's virus infection on the subsequent demyelinating disease in CBA mice

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**Abstract**

Chronic restraint stress, administered during early infection with Theiler's virus, was found to exacerbate the acute CNS viral infection in male and female mice. During the subsequent demyelinating phase of disease (a model of multiple sclerosis), the effect of stress on disease progression was sex-dependent. Previously stressed male mice had less severe behavioral signs of the chronic phase, better rotarod performance and decreased inflammatory lesions of the spinal cord, while the opposite pattern was observed in females. In addition, mice in all groups developed autoantibodies to MBP, PLP139-151 and MOG33-55.
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## 1. Introduction

MS is one of the most common demyelinating conditions of the central nervous system (CNS), effecting 350,000 people in the United States alone (Anderson et al., 1992). Though the etiology of MS remains unknown, both gender and psychological stress have been shown to play a role in the development of the disease (Ackerman et al., 2003; Anderson et al., 1992; Mohr and Cox, 2001; Mohr et al., 2004; Noseworthy et al., 2000; Runmarker and Andersen, 1995; Confavreux et al., 1998). Marked sex differences exist in the onset and progression of MS. There is a 2:1 female predominance of relapsing remitting MS (80% of MS cases), but the incidence of primary progressive MS is similar among men and women (Noseworthy et al., 2000). In contrast to the female predominance in the *incidence* of MS, males tend to have a more severe clinical course.

While it is difficult to obtain *experimental* evidence of the effects of stress on MS in humans, it is widely recognized that MS patients report periods of stress prior to the onset of the disease and before exacerbations of their symptoms. As early as 1877, Charcot reported that stressful experiences precipitated the onset of MS (Charcot, 1877). Many studies since Charcot's report have found that MS patients, as compared to healthy controls, or patients with other neurological disorders, report more stressful experiences prior to initial symptomatology (reviewed in Mohr and Cox, 2001). Additionally, longitudinal studies find stress to increase the chances of exacerbation of MS (Mohr and Cox, 2001; Ackerman et al., 2003). A recent meta-analysis of 14 studies investigating stress and MS that were published from 1965 to 2003 found a significant increase in the risk of disease exacerbation following a stressful life event (Mohr et al., 2004). The type of stress, however, may

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be important. While relatively moderate and chronic stressors seem to follow the pattern of stress-induced exacerbation of disease, severe stressors (e.g., war, see Nisipeanu and Korczyn, 1993) have been found to lower the rate of relapses of MS. Nisipeanu and Korczyn (1993) utilized an Israeli population of MS patients that had been under investigation prior to and following missile attacks during the Persian Gulf War. These patients reported significantly fewer relapses during this stressful period than any other period of time under investigation. The type or severity of the stressor in this instance may be the determining factor. Mohr et al. (2000) found less severe stressors such as increased conflict, disruption of routine and daily hassles to predict the risk of developing new brain lesions 8 weeks later, while there was no effect of severe stress on brain lesion development. Yet, Ackerman et al. (2003) found exacerbations in MS symptoms to be more likely following stressful life events, *independent* of type of stressor. Because the relationship between stress and MS in humans is complex, this research domain is likely to benefit from the investigation of stress using animal models.

Theiler's murine encephalomyelitis virus (TMEV) is a naturally occurring pathogen that was originally isolated from mice. TMEV infection results in Theiler's virus-induced demyelination (TVID) in susceptible strains of mice and is commonly used as an animal model of MS (for reviews, see: Dal Canto et al., 1995; Tsunoda and Fujinami, 1996; Oleszak et al., 2004). In the early stages of infection, TMEV causes a central nervous system infection (Theiler, 1937). Though typically asymptomatic, under conditions of immunosuppression, mice may display symptoms of encephalitis during this acute CNS infection (Campbell et al., 2001; Sieve et al., 2004). In susceptible strains of mice, the virus is not cleared from their CNS and a persistent CNS inflammatory demyelinating condition, similar to MS, follows the acute CNS viral infection (Lipton, 1975; Welsh et al., 1989; Tsunoda et al., 1997).

Previous studies have found that chronic restraint stress applied during the first four weeks of TMEV infection exacerbates this acute viral infection in male CBA mice (Campbell et al., 2001; Mi et al., 2004) and in male and female SJL mice (Sieve et al., 2004). In male and female SJL mice, this acute phase stress-induced exacerbation of the viral infection translated into an exacerbation of the subsequent chronic demyelinating phase of TMEV infection (Sieve et al., 2004). Though the same pattern of results was found in male CBA and SJL mice during the acute viral infection, there is reason to believe that the effect of restraint stress on the chronic demyelinating phase may vary across mouse strain. When nonstressed CBA and SJL mice are infected with TMEV, they do not display prominent behavioral signs of encephalitis or polio-like symptoms during early viral infection (Campbell et al., 2001; Sieve et al., 2004). Although acute phase symptomatology tends to be mild, the virus infects neurons and later glia cells and induces a persistent infection of the CNS that subsequently triggers demyelination. While 100% of SJL mice typically have viral persistence in the CNS and develop the chronic demyelinating phase of the disease, only 70% of CBA mice develop the chronic phase of the disease (for reviews, see: Friedman and Lorch, 1985; Oleszak et al., 2004). Simas and Fazakerley (1996) found that, when infected with $10^4$ pfu of the BeAn strain of TMEV, the resulting disease course of CBA mice could be separated into three categories: (1) death by acute encephalitis, (2) no clinical signs in the acute phase, but high viral titers in the acute phase that led to persistence of virus in the CNS throughout the chronic phase of the disease, and (3) no clinical signs and low viral titers in the acute phase, and no detectable virus after 28 days pi. Thus, while the outward symptoms of the acute viral infection in CBA and SJL mice may appear the same, underlying differences in viral persistence in the CNS may still exist.

To further investigate the interaction between sex and stress in the development of TVID, the present study examined whether administration of restraint stress during acute infection with TMEV alters the course of the chronic demyelinating disease in male and female CBA mice. Thus, we evaluated the effects of restraint and sex on behavioral, histological and immunological manifestations of acute and chronic disease.

## 2. Materials and methods

### 2.1. Subjects

Male ($n=12$) and female ($n=12$) CBA mice were obtained from Harlan (Houston, TX) at 3 weeks of age. All mice were housed 3 per cage with food and water available ad libitum. Male and female mice were housed in separate rooms with separate ventilation systems. They were allowed to acclimate to their environment for 1.5 weeks prior to infection, during which time they were handled at least twice by all experimenters involved in the study, and baseline measures were obtained. All animals were housed in accordance with Texas A&M University and National Institutes of Health animal care guidelines.

### 2.2. Infection

The BeAn strain of TMEV (obtained from Dr. H.L. Lipton, Department of Neurology, Northwestern University, Chicago, IL) was propagated and amplified in BHK-21 cells. The culture supernatant containing infectious virus was aliquoted and stored at −70 °C before use (Welsh et al., 1987). As in previous studies, mice were infected at 4.5 weeks of age. Following isoflurane anesthetization (Vedco Inc., St. Joseph, MO), $5\times10^4$ pfu (plaque forming units) of BeAn strain in a 20 μl volume was inoculated into the right mid-parietal cortex at a depth of approximately 1.5 mm. The non-infected mice received a similar injection of 20 μl of

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