



The John Whitaker
Track





EFFECT OF DELETION OF IL-4/IL-4RA IN EXPERIMENTAL AUTOIMMUNE ENCEPHALOMYELITIS (EAE)

Anti-inflammatory cytokines like interleukin-4 (IL-4) favor a T helper-type 2 (Th2) immune response over a Th1 type. This study examines the impact of lack of either IL-4 or its receptor subunit alpha (IL-4Ra) on EAE in Balb/c mice. EAE is thought to be driven by a myelin-specific Th1 response. Previous studies showed that deletion of IL-4 led to more severe EAE and poor Th2 mediated remissions. To compare the relative effect of IL-4 receptor and ligand deletion on EAE, we used Balb/c IL-4Ra-deficient mice in parallel with Balb/c IL-4^{-/-}. IL-4R is a heterodimer, also used by IL-13, another Th2-related cytokine. Interestingly, after immunization with CNS myelin, Balb/c mice developed either typical or atypical signs of EAE, the latter showing almost normal tail tone and limb paralysis. The ratio of atypical/typical EAE was dramatically higher in IL-4Ra^{-/-} mice compared to IL-4^{-/-} and wt. IL-4Ra^{-/-} animals developed moderate EAE, while IL-4^{-/-} and wt displayed comparable severe signs. Cumulative EAE scores reflect delayed disease onset in deficient animals compared to wt. However, IL-4^{-/-} mice showed poorer recovery than wt and IL-4Ra^{-/-}. These findings suggest that factors other than IL-4 contribute to disease progression in EAE. Histopathology revealed that lack of IL-4 or IL-4Ra did not alter CNS infiltration and demyelination in animals displaying EAE, nor did it affect the ability to remyelinate.

Ongoing cytokine quantification at protein and mRNA levels will be presented and support an imbalanced Th1/Th2 ratio. However, the presence of comparable titers of IgG2a, IgG2b, IgG1 and IgE in wt, IL-4Ra^{-/-} and IL-4^{-/-} mice, did not suggest a lack of isotype switching.

We conclude that the impact of IL-4Ra and its ligand, might be strain-specific, and that in Balb/c, deletion of IL-4 and to a greater extent, IL-4Ra, ameliorates EAE.

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AN RCT WITH OPEN-LABEL EXTENSION OF SATIVEX, A CANNABIS-BASED MEDICINE (CBM) IN MS-RELATED CENTRAL PAIN

Objective: To compare the efficacy and tolerability of Sativex, a whole plant cannabis based medicine (CBM) with placebo in the relief of central neuropathic pain (CP) due to MS and to investigate the long-term safety and efficacy of CBM in this setting.

Design / Methods: The efficacy and tolerability of Sativex, which contains D-9 tetrahydrocannabinol (THC) and cannabidiol (CBD), was investigated in a randomized, double-blind, placebo-controlled, parallel-group trial of 66 MS patients with CP. Sixty-four patients (96.9%) completed the randomized study (4 weeks), and 63 entered a long-term, open-label extension study (95.5%). CBM was administered as an oromucosal spray, each spray delivering 2.7mg THC and 2.5mg CBD. Patients were allowed to self-titrate their dosage. Patients were maintained on their existing analgesic medications.

Results: In the randomized trial, CBM achieved significant improvements in pain (NRS-11, $p=0.005$ and Neuropathic Pain Scale $p=0.044$) and sleep disturbance (NRS-11, $p=0.003$) compared to placebo. The mean NRS-11 pain scores at baseline were: CBM = 6.5, placebo = 6.4 and CBM = 3.8, placebo = 4.9 in the last week of the randomized trial. Sixty two patients entered the open-label trial immediately. At the time of this analysis, the mean duration of treatment was 463 days in the open-label trial ($n=63$; median = 638, range = 3 – 917). Sustained improvement in pain scores was observed in 21 patients who entered the extension study and reached 92 weeks of CBM treatment (mean NRS score = 3.16). There was no evidence of tolerance to CBM (mean sprays per day = 7.73 at open-label entry, 6.11 in last seven days of treatment).

Conclusions / Relevance: Sativex is efficacious and well tolerated as a treatment for CP due to MS for at least 12 months with no evidence of tolerance.

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ARE SYMPTOMS ASSOCIATED WITH PHYSICAL ACTIVITY IN MULTIPLE SCLEROSIS?

Background: Multiple sclerosis (MS) results in a wide range of sensory, motor, visual, bladder, sexual, and psychological symptoms. The symptoms might be associated with a reduction in physical activity behavior among those with MS. Based on Nagi's disablement model and social-cognitive theory, the relationship between symptoms and physical activity might be accounted for by functional limitations and self-efficacy. **Purpose:** The present study examined the possibility that MS-related symptoms are inversely associated with physical activity, and then examined the roles played by functional limitations and self-efficacy in the relationship between symptoms and physical activity. **Methods:** The sample consisted of 196 individuals with a definite diagnosis of MS from the Midwest region of the United States. The individuals completed a battery of questionnaires and then wore an accelerometer for a 7-day period. The battery of questionnaires included measures of physical activity, MS-related symptoms, self-efficacy and functional capacity. The data were analyzed using covariance modeling in AMOS 5.0. **Results:** There was an initial moderate inverse correlation between symptoms and physical activity ($\beta = -.43$). Subsequent analyses indicated that symptoms had a direct effect relationship with functional limitations ($\beta = -.66$); functional limitations had direct relationships with self-efficacy ($\beta = .31$) and physical activity ($\beta = .48$); self-efficacy had a direct relationships with physical activity ($\beta = .33$). **Conclusion:** Symptoms were associated with reduced physical activity in this sample of people with MS, and the relationship was accounted for by functional limitations and self-efficacy. Our findings support the application of Nagi's disablement model and social-cognitive theory for understanding the relationship between symptoms and physical activity in those with MS.

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CONTRASTING ROLES OF AXONAL DEGENERATION IN AUTOIMMUNE VERSUS VIRAL MODELS FOR MS

Although demyelination is a cardinal feature in multiple sclerosis (MS), axonal injury also occurs. In Theiler's murine encephalomyelitis virus (TMEV) infection, an animal model for MS, axonal injury precedes demyelination. We hypothesize that initial axonal injury may alter the local microenvironment and recruit inflammatory cells, contributing to demyelination. Here, lesions develop from the inside (axon) to the outside (myelin) (Inside-Out Model). We tested whether the delay of axonal degeneration could affect the disease severity in autoimmune and viral models for MS: experimental autoimmune encephalomyelitis (EAE) and TMEV infection. We compared wild-type C57BL/6 (B6) mice with C57BL/Wld^s (Wld) mice that carry a mutation that delays axonal degeneration. Both mouse strains were sensitized with myelin oligodendrocyte glycoprotein (MOG)₃₅₋₅₅ peptide, and showed a similar onset of EAE, 2 weeks post immunization (p.i.). However, during the chronic stage, Wld mice recovered completely with small areas of demyelination, while B6 mice continued to show paralysis with large demyelinating lesions. MOG specific lymphoproliferative responses in Wld mice were similar at 2 weeks p.i. but lower during the chronic stage, compared with B6 mice. B6 mice and Wld mice developed axonal degeneration 2 weeks and 2 months p.i., respectively. In TMEV infection, while no B6 mice showed paralysis, 30 and 50% of Wld mice showed paralysis during the acute and chronic stages. Wld mice developed higher levels of inflammation, virus antigen positive cells and TMEV specific lymphoproliferative responses, compared with B6 mice. Since TMEV can use axons to spread in the brain, axonal degeneration in B6 mice might be a beneficial self-destructive mechanism that limits the virus spread, while slow axonal degeneration in Wld mice could favor virus spread. Therefore, axonal injury can play contrasting roles (beneficial versus detrimental) depending on the type of disease. The caution should be taken with a therapeutic strategy targeting axonal degeneration.

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ANTIGEN-SPECIFIC TREATMENT OF EAE REVERSES MYELIN AND AXONAL INJURY

Inflammation results in CNS injury in multiple sclerosis (MS) and experimental autoimmune encephalomyelitis (EAE), an animal model of MS. It is uncertain how much repair of injured myelin and axons can occur following highly effective anti-inflammatory therapy in EAE and MS. In this study, thus, SJL mice with relapsing-remitting EAE were treated with an antigen-specific Recombinant T cell receptor Ligand (RTL) RTL401, a mouse I-As/PLP139-151 construct, after the peak of EAE, and euthanized at different time points to assess the levels of neuroinflammation, myelin and axon damage in their spinal cords. Our result showed that RTL401 administered after the peak of acute EAE prevented further relapses and induced a marked reduction in inflammation and hyaluronan in the CNS, associated with a reversal of myelin and axonal injury. Electron microscopy showed that RTL-treated mice had reduced pathology compared with mice treated with vehicle and mice at the peak of disease, as demonstrated by a decrease in continued degeneration, increase in remyelinating axons and the presence of an increased number of small, presumably, regenerative axonal sprouts. These findings suggest that RTL therapy may be neuroprotective or neuroregenerative in EAE and by implication, MS.

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RELATING SENSORIMOTOR FUNCTION AND TRACT SPECIFIC MRI IN MULTIPLE SCLEROSIS

Conventional magnetic resonance imaging (MRI) techniques provide a means for diagnosing multiple sclerosis (MS) and identifying new MS lesions. However the correlation between conventional MRI and clinical symptoms of MS is imperfect, perhaps because conventional MRI only poorly characterizes the underlying demyelination and axonal damage. We hypothesize that magnetization transfer (MT) and diffusion tensor imaging (DTI), which are sensitive to white matter fiber tract integrity, will predict of specific sensorimotor impairments.

We performed MT and DTI using a 3T Philips GyroscanNT (Best, The Netherlands) system in individuals with MS (with acute or chronic lesions) and controls. We also acquired and coregistered axial T1 (pre- and post- contrast), double echo T2, FLAIR, and MPRAGE images. Custom written software was used for fiber tract reconstruction. MR parameters such as T2, fractional anisotropy (FA), mean diffusivity, and MT ratio were calculated along various tracts, including the corticospinal tract. Sensorimotor impairments were evaluated using quantitative balance (force plate), walking (Optotrak 3-D), vibration sense (Vibratron), and strength (dynamometer) tests that relate to specific white matter tracts.

Our subjects show variable sensorimotor impairments and lesions, typical of MS patients. Our data show that MT and DTI, in combination, provide a sensitive way to measure white matter tracts and define lesion characteristics *in vivo*. Results show significant correlations of FA in the corticospinal tract with ankle strength ($r=0.4$, $p<0.05$) not vibration sense ($r=-0.01$). Correlations with conventional MRI and ankle strength are lower and not significant (i.e., T2, $r=-0.09$; T1, $r=0.19$). This is a first step toward relating structure and function in MS while gaining theoretical and practical insights into rehabilitation. We expect that information from these studies could be used to evaluate efficacy of medical therapeutic interventions and rehabilitative strategies.

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