MyMD-1: Potential treatment for MS Depression

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ABSTRACT

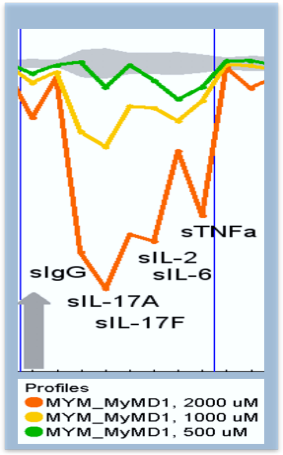
MyMD1, an orally bioavailable immune system regulator, has a host of unique properties suggesting that it could be an ideal treatment of autoimmune diseases and the psychiatric comorbidities associated with these conditions. To demonstrate the scientific rationale to support the use of MYMD-1 as an effective treatment for immune-mediated depression, such as Multiple Sclerosis (MS), we needed to develop a model that recapitulated key aspects of MS and simultaneously provided a means of testing antidepressant activity. We chose LPS-induced immune activation associated with depressive behavior in mice, assessed using FST to demonstrate antidepressant activity of MYMD-1 as a model for the treatment of MS Depression. TNF-α, IL-6 and IL-17 are potently inhibited by MYMD-1, making LPS a potentially ideal model. We present here our preclinical findings of the ability of MYMD-1 to treat immune-mediated depression.

INTRODUCTION

Lipopolysaccharide (LPS) has been used for over 45 years in preclinical and ex-vivo models of MS. LPS is a cell-wall immunostimulatory component of gram-negative bacteria and was first identified as a Toll-like receptor 4 (TLR-4) ligand. TLR-4 is primarily expressed on microglia but also CD4+ T cells in the central nervous system, which once activated, produce proinflammatory cytokines, including TNF-α, IL-6 and IL-17. LPS has been shown to not only model key aspects of MS, but also to be intimately linked to the pathophysiology of this autoimmune CNS disease. LPS has also been implicated in MS depression through an inflammatory pathway. Blood cells purified from MS patients with depression produced much higher levels of various cytokines in response to LPS stimulation, including IL-6 and IL-17, than cells purified out of non-depressed MS patients. Moreover, acute activation of the peripheral innate immune system in laboratory animals, through the administration of the cytokine inducer LPS has been previously studied and shown to induce depressive-like behavior, as measured by increased immobility in the forced swim test (FST). The sensitivity to a broad range of antidepressant drugs that makes the FST a suitable screening test and is one of its most important features leading to its high predictive validity.

OBJECTIVES

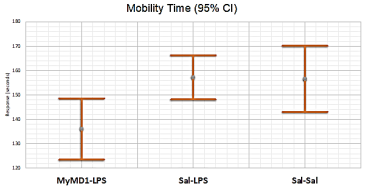
We set out to test the following paradigm to see if MYMD-1 would effectively treat MS Depression in a preclinical paradigm: 1) we employed LPS to model the inflammatory changes found in MS, 2) we utilized the FST that has been shown to model antidepressant effects of various drugs, 3) we predicted that MYMD-1 would not behave like an antidepressant in untreated mice (because it is not an antidepressant for all types of depression), 4) we further predicted that in LPS treated mice that MYMD-1 would have antidepressant-like effects (thereby demonstrating that our drug only works in a subset of depression modeled after the inflammatory changes seen in MS).



METHODS

Male and female C57Bl/6 mice were tested between 10-12 weeks of age. Each group had n=5-7. Mice were administered an i.p. injection of saline or 100mg/kg MyMD-1 at 10am each morning for four consecutive days. On the fourth day, 1 hour after injection of saline or 100mg/kg MyMD-1, mice were administered saline or 1mg/kg LPS. 24 hours following injection mice were weighed and tested in the open field and forced swim test. No additional injections were given on the fifth day. Open field: Locomotor activity was assessed over 30 minutes in a 40x40cm activity chamber with infrared. Horizontal activity, as well as time spent in the center or periphery of the chamber, was automatically recorded. Forced Swim test: Mice were placed in a cylinder of water for six minutes. Mobility time during the last four minutes of the test was scored, and immobility time was calculated.

MYMD-1 Decreases Immobility in Forced Swim Test of LPS-Induced Depression Model



ANOVA					
Source of Variation	d.f.	SS	MS	F	p-value
Between Groups	2	3,903	1,952	5	0.011
Within Groups	36	13,798	383		
Total	38	17,702			

Tukey-Kramer	Difference	Test Statistic	p-value
MYMD1-LPS vs Sal-LPS	-21.159	3.968	0.021
MYMD1-LPS vs Sal-Sal	-20.512	3.766	0.030
Sal-LPS vs Sal-Sal	0.647	0.117	0.996

RESULTS

The addition of LPS by itself had no effect on immobility time. The addition of MYMD-1 by itself had no effect on immobility time compared to saline injected mice for 4 consecutive days. Treatment with MYMD-1 decreased immobility when LPS was given, consistent with it having an antidepressant response. To rule out pharmacological effects on general motor activity that might account for behavioral patterns in the forced-swim test, the open-field test is often used in conjunction with the forced-swim test to assess locomotor activity. MYMD-1 treatment had no effect on open field testing.

CONCLUSIONS

Our initial tests revealed that since an antidepressant response to MYMD-1 was only seen in LPS treated mice, which models inflammatory changes seen in MS, these results are consistent with MYMD-1 demonstrating effective antidepressant effects in a subset of depression—i.e., depression associated with MS.

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