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Curcumin aggravates CNS pathology in experimental systemic lupus erythematosus

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ABSTRACT

Complement activation and inflammation are key disease features of systemic lupus erythematosus. Curcumin is an anti-inflammatory agent that inhibits the complement cascade. Therefore, we hypothesized that curcumin will be protective in CNS lupus. To assess the effect of curcumin on CNS-lupus, MRL/*lpr* mice were used. Brain MRI showed that curcumin (30 mg/kg body wt. i.p. from 12–20 weeks) worsened regional brain atrophy. The volumes of the lateral and third ventricles are significantly increased (150%–213% and 107%–140%, without and with treatment respectively compared to MRL+/+ controls). The hippocampus was reduced further (83%–81%) by curcumin treatment. In line with increased brain atrophy, there were edematous cells (41% increase in cell size in MRL/*lpr* compared to MRL+/+ mice. The cell size was further increased by 28% when treated with curcumin; $p<0.02$) in the cortex. In line with increased atrophy and edema, there was a significant increase ($p<0.02$) in the mRNA and protein expression of the water channel protein, aquaporin 4 in these mice. The increase in the matrix proteins, glial fibrillary acidic protein and vimentin in lupus mice in the hippocampus was prevented by curcumin. Curcumin increased IgG deposits and decreased C3 deposits in brain with a corresponding increase in immune complexes and decrease in C3 concentration (by 60% in MRL/*lpr* mice Vs. MRL+/+ mice and a further 26% decrease when treated with curcumin) in circulation. Decrease in C3 could alter the transport of immune complexes leading to an increase in IgG deposits which could induce inflammatory pathways thereby leading to worsening of the disease. The neurological outcome as measured by maze performance indicates that the curcumin treated mice performed poorly compared to the untreated counterparts. Our results for the first time provide evidence that at the dose used in this study, curcumin aggravates some CNS disease manifestations in experimental lupus brain. Therefore, until a safe dose range is established by additional studies, and the validity of the findings is

Abbreviations: SLE, system lupus erythematosus; CNS, central nervous system; CMN, curcumin; GFAP, glial fibrillary acidic protein; MAC, membrane attack complex; MRL/*lpr*, MRL/MpJ-*Tnfrsf6*$^{lpr/lpr}$; MRL+/+, MRL/MpJ-*Tnfrsf6*$^{+/+}$; MRI, magnetic resonance imaging; IF, immunofluorescence; AQP4, aquaporin 4

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determined in human patients, caution may be warranted in the use of curcumin, even as adjuvant therapy for CNS lupus.

1. Introduction

Systemic lupus erythematosus (lupus) is a devastating autoimmune disorder associated with characteristic neuropathological changes, including neuronal loss, edema, vasculitis, and inflammation resulting in behavioral changes, with no effective treatment (Cieslik et al., 2008; West, 1996; Abbott et al., 2003; Abel et al., 1980; Appenzeller et al., 2005). Research identifying new therapeutic agents that are innocuous is of high priority and urgently needed. Earlier studies from our laboratory show a close association between complement activation and CNS injury in lupus (Alexander et al., 2005). The complement cascade is normally protective but uncontrolled activation of the complement system makes it destructive. In addition, complete complement inhibition can leave the patient open to infections. Therefore it is important to identify an efficacious and less toxic therapeutic target for the treatment of CNS lupus. Since curcumin (CMN), a commonly used culinary spice was recently shown to inhibit both classical and alternative pathways (Kulkarni et al., 2005b), we hypothesized that CMN treatment may improve outcome following CNS lupus.

CMN isolated from the rhizomes of the plant, *Curcuma longa* L. Zingiberaceae (Motterlini et al., 2000;Wang et al., 2008) interacts with a number of signaling targets involved in inflammation and other biological processes. CMN has a variety of pharmacological activities, and is used to treat a number of diseases associated with inflammation, oxidative damage, proliferation, fibrogenesis and cognitive deficits (Motterlini et al., 2000;Mehta et al., 1997;Wang et al., 2008). Studies in experimental models suggest that CMN treatment can protect against Alzheimers disease and focal cerebral ischemia, and was shown to cross the BBB (Jiang et al., 2007;Kaur and Ling, 2008;Yang et al., 2005;Balasubramanian, 2006; Garcia-Alloza et al., 2007). This study will attempt to determine the effects of CMN treatment in lupus, using the well established lupus model, MRL/*lpr* mice.

MRL/*lpr* mice have several disease modalities that are similar to human SLE and therefore it is a widely used and accepted model, although the disease in the mice is progressive while patients have disease flares (Theofilopoulos et al., 1989; Theofilopoulos and Dixon, 1985). They have a number of clinical and pathological features that show close similarity to human lupus, including structural and behavioral changes (Ainiala et al., 2005); (Alexander et al. 2007;Alexander and Quigg, 2007;Ballok, 2007;Diamond et al., 2006). In accordance with the suggestion by researchers at Stanford University (Beaudreau and O'Hara, 2008), that a symbiotic relationship exists between anxiety and cognition (Diamond et al., 2006;Kozora et al., 2005), both patients and MRL/*lpr* mice demonstrate anxiety and cognitive impairment (Sakic et al., 2005;Schrott and Crnic, 1996;Szechtman et al., 1997). MRI imaging studies revealed diffuse brain injury, brain atrophy, altered hippocampus and axonal loss in both patients and MRL/*lpr* mice (Aisen et al., 1985;Peterson et al., 2005;Graham and Jan, 2003;Peterson et al., 2005). Our earlier studies demonstrated increased water content in MRL/*lpr* brain similar to edema in patients (Alexander et al., 2003). In line with the decreased levels of N-acetylaspartate, a marker of neuronal viability in patients, increased TUNEL staining, DNA laddering and Fluoro Jade B positivity are observed in MRL/*lpr* brains (Ballok et al., 2003;Sakic et al., 2000;Alexander et al., 2005).

A major challenge in lupus treatment has been developing clinically efficacious therapeutic agents, with no side effects. With experimental evidence identifying multiple protective mechanisms of CMN, and studies demonstrating its effectiveness in alleviating several diseases, the role of CMN as a novel therapeutic approach for lupus disease merits exploration. Our results show that contrary to our expectations and results obtained in other disease settings such as multiple sclerosis, CMN caused a worsening of disease in MRL/*lpr* mice. Our results demonstrate that in lupus setting CMN has to be used with caution even as an adjuvant therapy.

2. Results

These studies focused on brain MRI assessments and water content, the immune system specifically C3 and IgG, and behavior in treated and untreated lupus mice. Our results demonstrate that curcumin treatment increases brain atrophy, aquaporin 4 expression and astrocytosis. These alterations could be due to the decrease on the central complement protein C3 leading to increased IgG deposits which could activate or amplify different inflammatory pathways in MRL/lpr mice.

2.1. *Curcumin aggravates brain atrophy in MRL/lpr mice*

MRI studies are important to understand the translational potential of the results obtained in MRL/*lpr* mice. Similar to earlier studies (Sakic, 2009, (Prendiville et al., 2003)), imaging showed an increase in MRL/ *lpr* mice total brain volume, although it did not reach statistical significance (Table 1). The atrophy manifested as enlarged lateral ventricles compared to MRL+/+ controls (Fig. 1). In contrast, the hippocampal volume is significantly reduced ($p<0.05$) in MRL/*lpr* mice which is consistent with the observations in SLE patients (Ballok, 2004). Contrary to our expectations, CMN aggravated these features further, causing a significant increase in lateral ventricle compared to control MRL+/+ mice and substantial increase in the volume of the third ventricles and a further decrease in hippocampal volume in MRL/*lpr* mice (Table 1). In brief, the MRI studies show that although CMN treatment reduced the global brain volume compared to the MRL/*lpr* mice, it significantly increased the lateral and third ventricles and further decreased the hippocampal volume compared to MRL+/+ mice.

2.2. *Curcumin causes histological changes in lupus brain in a region specific manner*

In line with the imaging studies, lupus brain was altered with increased edematous cells in the cortex. Histological studies