Annals of General Psychiatry

BioMed Central

Poster presentation

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Chronic anti-inflammatory treatment fails to prevent CNS disease in lupus-prone mice

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from International Society on Brain and Behaviour: 2nd International Congress on Brain and Behaviour
Thessaloniki, Greece. 17–20 November 2005

Published: 28 February 2006

Annals of General Psychiatry 2006, **5**(Suppl 1):S212 doi:10.1186/1744-859X-5-S1-S212

Background

Spontaneous development of systemic inflammation and autoimmunity results in brain atrophy and behavioral dysfunction in lupus-prone MRL-lpr mice. Based on beneficial effects of non-steroidal anti-inflammatory drugs in other CNS inflammation models, we test the hypothesis that chronic treatment with ibuprofen (COX-1/COX-2 inhibitor) attenuates behavioral deficits and neuronal loss in this model of neuropsychiatric lupus.

Materials and methods

To avoid confounding effects of repeated injections on performance in behavioral tasks, ibuprofen was provided in rodent chow from 5–19 weeks of age and an established behavioral battery was concurrently applied. Neuropathological and immunological parameters were estimated upon sacrifice using F4/80, CD3, and Fluoro Jade B (FJB) staining techniques. Transmission electron microscopy (EM) was also employed to the examine ultrastructural features of neurodegeneration in murine brains.

Results

The density of F4/80-positive microglial cells was increased in brains of MRL-lpr mice fed with the control diet, but the treatment with ibuprofen neither prevented this activation nor normalized their behavioral performance. Similarly, no attenuation in infiltration of CD3-positive lymphocytes into the choroid plexus or density of dying (FJB-positive) neurons were seen. Paradoxically, ibuprofen increased serum levels of TNF-alpha and circulating immune complexes in both MRL-lpr and the less symptomatic MRL +/+ substrain. However, it did not promote lymphocyte infiltration into the brain or neurodegeneration in MRL +/+ control mice. EM revealed numerous dark neurons in MRL-lpr brains, but no evidence of blebbing of the nucleus or apoptotic bodies was found.

Discussion

Taken together, present results suggest that activation of COX-dependent inflammatory pathways is not critical in the etiology of CNS dysfunction in MRL-lpr mice. Furthermore, modest amplification in systemic TNF-alpha levels do not seem to compromise the permeability of the blood-brain barrier, a condition proposed to be instrumental for CNS degeneration and behavioral dysfunction during lupus-like disease. Contrary to our expectation, nonapoptotic mechanisms appear to predominate the neuronal death in lupus mice.

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