Intrathecal methotrexate reduces demyelination and astrogliosis in a non-inflammatory demyelination model

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Objective:

We hypothesize that the benefits of intrathecal methotrexate (ITMTX) on progressive MS is only partially related to its anti-inflammatory properties. Consequently, we investigated its influence on a non-inflammatory CNS demyelination model.

Background:

MS patients with a progressive disease respond poorly to currently available anti-inflammatory disease modifying agents. Intrathecal administration of the antifolate drug methotrexate has a beneficial impact on the disease progression of severe primary and secondary progressive MS cases. Astrocytic activation and subsequent astrogliosis occur in progressive MS as well as in the cuprizone-induced model of corpus callosum demyelination and are considered to be hallmarks of scar formation in the CNS.

Methods:

To induce corpus callosum demyelination, male C57Bl/6 mice were fed with cuprizone mixed into ground chow. Methotrexate was administered intracerebroventricularly (icv) by osmotic pumps. Brain tissue sections were stained for astrocytic markers, myelin and microglial cells. Random sections were analysed per animal by a blinded investigator.

Results:

After being fed with cuprizone for four weeks, mice were characterized by strong demyelination and an increase in GFAP+ astrocytes and MAC3+ microglial cells within the corpus callosum as compared to naive mice. ITMTX significantly decreased the demyelination and number of astrocytes in the corpus callosum. ITMTX starting after two weeks of cuprizone administration also decreased astrogliosis and microglial activation in the corpus callosum at the end of six weeks of cuprizone administration. Contrastingly, an icv administration of methotrexate after a cuprizone feeding period of 6 weeks neither delayed remyelination nor influenced the number of astrocytes or microglial cells in the corpus callosum.

Discussion:

The pathophysiological basis of the cuprizone-induced demyelination model are not primarily related to inflammatory mechanisms. Similarly, the progressive forms of MS are less dependent on inflammatory events than its relapsing forms. We were able to establish an inhibition of demyelination and astrogliosis by ITMTX in the corpus callosum of cuprizone fed mice. This corroborates that the beneficial impact of ITMTX on disease progression is not solely mediated by its anti-inflammatory properties. Moreover, the inhibition of astroglial activation suggests that ITMTX may influence the generation of astrocytic scars in MS lesions.