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MULTIPLE SCLEROSIS

Drug-enhanced remyelination in a multiple sclerosis model

Benztropine, a drug that is already approved for the treatment of Parkinson disease, has been identified as a potential new therapy for multiple sclerosis (MS). In experimental models of MS, benztropine induced the differentiation of oligodendrocyte precursor cells (OPCs), and enhanced remyelination. Alone or in combination with other pharmacotherapies, the drug reduced disease severity in mice with experimental autoimmune enchephalitis (EAE).

MS is characterized by acute and chronic phases of demyelination in the CNS, with limited remyelination between episodes. To identify small drug-like molecules that selectively induce OPC differentiation, a research team led by Brian Lawson, Peter Schultz and Luke Lairson from the Scripps Institute, California, developed a high-throughput imaging assay of myelin basic protein expression (MBP) in primary OPCs derived from the rat optic nerve.

Benztropine was the most effective molecule in inducing OPC differentiation and increasing transcript levels of MBP and myelin oligodendroglial glycoprotein (MOG). The drug also increased the numbers of MBP-positive oligodendrocyte processes and axons *in vitro*, suggesting that it enhances oligodendroctye maturation and promotes remyelination.

Pharmacological analyses revealed that the mechanism of action of benztropine depends on muscarinic receptor antagonism. The drug most probably binds to M1/M3 receptors on oligodendrocytes, which in turn stimulates remyelination.

The researchers showed that in the EAE model of MS, prophylactic treatment with benztropine decreased the severity of the acute phase and virtually eliminated the relapse phase of the disease compared with vehicle-treated controls. Remyelination was evident even during the active phase of EAE. Benztropine had no effect on T-cell activation and proliferation *in vivo*, or on T-cell development after adoptive transfer of EAE, indicating that its effects on remyelination were mediated through enhanced differentiation of oligodendrocytes rather than inhibition of the immune response.

> “Remyelination was evident even during the active phase of EAE”

Treatment with benztropine decreased the clinical severity of EAE better than or equally to FTY720, which affects T-cell trafficking and is already used in the treatment of MS. In combination with a suboptimal dose of FTY720, benztropine significantly reduced the severity of EAE compared with FTY720 alone. This result was probably attributable to the additive effects of immunosuppression by FTY720 and induction of remyelination by benztropine.

The addition of a drug such as benztropine to the MS treatment regimen has the potential to reduce the amounts of other drugs used in MS therapy that are known to have serious adverse effects. Further preclinical and therapeutic evaluation of benztropine is required, but the current study provides hope of a new therapeutic avenue for patients with MS.

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Original article Deshmukh, V. A. *et al.* A regenerative approach to the treatment of multiple sclerosis. *Nature* doi:10.1038/nature12647