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AUTOIMMUNE DISEASE

Parkinson's drug promotes myelin repair

Multiple sclerosis (MS) is an autoimmune disease of the central nervous system (CNS) that is characterized by immune cell infiltration and inflammation, which cause neuronal demyelination and degeneration. Accordingly, MS therapy largely involves the long-term use of disease-modifying injectable immunosuppressants or immunomodulators, but these are associated with significant side effects and variable efficacy. Now, writing in *Nature*, Deshmukh and colleagues report that a drug currently approved for the treatment of Parkinson's disease promotes neuronal myelination and decreases the clinical severity of MS in mouse models.

Neuronal remyelination is mediated by the generation of new myelinating oligodendrocytes from oligodendrocyte precursor cells (OPCs). Although patients with MS have sufficient OPCs that are capable of migrating to sites where myelination is required, these precursor cells fail to differentiate into myelin-producing cells, thereby promoting disease progression.

Therefore, Deshmukh and colleagues set out to identify drug-like small molecules that selectively induced OPC differentiation. Using a high-content imaging assay based on the induction of myelin basic protein (MBP) expression — a marker of mature myelin-producing oligodendrocytes — in primary rat optic nerve-derived OPCs cultured under basal differentiation conditions, they screened a collection of 100,000 structurally diverse molecules.

The most effective inducer of OPC differentiation was benztropine, which the authors chose to investigate further because it is well established as an approved treatment for Parkinson's disease. Further *in vitro* studies in mouse OPCs co-cultured with mouse embryonic-stem-cell-derived neurons confirmed that benztropine induced OPC differentiation and promoted myelination.

Next, they explored the mechanisms mediating these beneficial actions of benztropine. Considering the known actions of the drug, they investigated the effect of selective agonists of muscarinic acetylcholine receptors (mAChRs) or nicotinic acetylcholine receptors (nAChRs) — carbachol or nicotine, respectively — on benztropine activity. They found that carbachol prevented benztropine from inducing OPC differentiation *in vitro*. Further analysis revealed that the effect of benztropine on OPCs was dependent on specific antagonism of M1 and/or M3 mAChRs.

In vivo, daily intraperitoneal injection of benztropine decreased the clinical severity of the acute phase of the disease and virtually eliminated the relapse phase in both prophylactic and therapeutic experimental autoimmune encephalomyelitis (EAE) mouse models of MS without exhibiting signs of general toxicity. In fact, the decrease in clinical disease severity observed with benztropine was comparable to that achieved with the immunosuppressive MS drugs fingolimod or interferon-β. Furthermore, the combination of suboptimal doses of benztropine and fingolimod similarly decreased disease severity, which may prove to be clinically relevant as fingolimod is associated with dose-dependent bradycardia.

Finally, analysis of spinal cords from drug- or vehicle-treated EAE mice revealed that benztropine caused significant remyelination without affecting the infiltration, abundance or demyelinating activity of inflammatory effector immune cells. In addition, benztropine did not affect T cell development or function in EAE mouse models (including an adoptive transfer model), and it enhanced OPC differentiation and accelerated remyelination in the immune-cell-independent cuprizone-induced mouse model of demyelination, which provides further support that the effects of benztropine were due to remyelination and not immunosuppression.

These findings support the potential of combining a remyelination enhancer with current immunosuppressive drugs as an effective therapeutic approach for the treatment of MS, and highlight benztropine as a promising lead compound.

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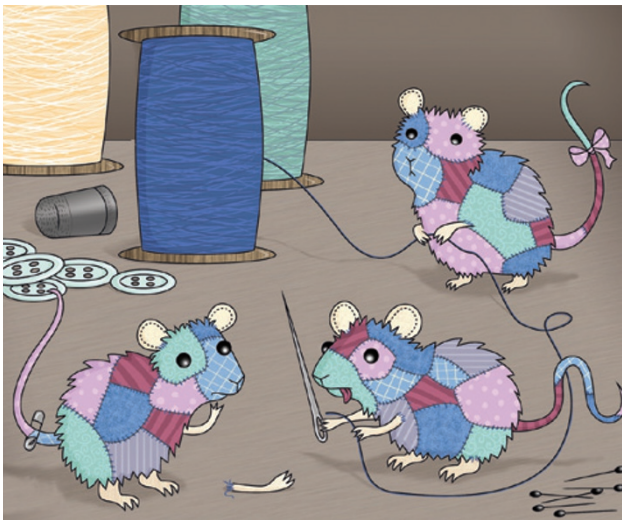

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ORIGINAL RESEARCH PAPER Deshmukh, V. A. *et al.* A regenerative approach to the treatment of multiple sclerosis. *Nature* **502**, 327–332 (2013)