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Combinatorial treatment strategies attenuate experimental autoimmune encephalomyelitis

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Multiple sclerosis (MS) is a chronic demyelinating disease of the central nervous system (CNS) characterized by inflammation and neurodegenerative processes. Currently, MS therapy involves the long-term use of immunomodulators, which tend to have numerous side effects and varying efficacies among MS patients. Additionally, these immunomodulators do not aid in promoting remyelination, which is essential to the return of neuronal function. Benztropine, a FDA-approved drug used for treatment of Parkinson's disease was recently identified as an effective inducer of oligodendrocyte precursor cell (OPC) differentiation in vitro and in experimental autoimmune encephalomyelitis (EAE), the most common animal model used to study MS. Thus, we sought to study the synergy of benztropine and tuftsin, immunomodulatory tetrapeptide shown to polarize microglia to the M2 phenotype in a MOG-induced acute EAE model. We examined effects on disease course, demyelination and microglial infiltration and polarization. Here we show that combinatorial treatment with both benztropine and tuftsin seems to markedly ameliorate the EAE disease course. Further, this treatment strategy reduces the pathological hallmarks of MS as well as these animals have reduced demyelination and decreased microglial activation with overall anti-inflammatory immune phenotype. This work has the potential to improve treatment strategies for patients with MS because cooperativity of these drugs will work to not only limit damage but also reverse it.

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Repeated *Streptococcus pyogenes* infections induce an autoimmune Th17 cell phenotype in the brain and impair blood-brain barrier integrity: A mouse model for PANDAS

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Streptococcus pyogenes infections are associated with two autoimmune diseases of the CNS: the movement disorder Sydenham's chorea and the neuropsychiatric syndrome PANDAS (Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcus infections). This bacterium is known to induce autoreactive, mimetic antibodies against several CNS targets. Delivery of such antibodies in the mouse brain induces behavioral and motor deficits that are reminiscent of PANDAS symptoms, supporting their causal role in this disease. How such autoreactive antibodies cross the blood-brain barrier (BBB) to attack CNS targets, however, is unknown. We have found that intranasal *S. pyogenes* infections lead to an antigen-specific Th17 cell response in the nasal associated lymphoid tissue (NALT), a functional analog of human tonsils. Repeated infections drive those cells towards an IL-17+ IFN-γ^+ phenotype that has been implicated in BBB breakdown during many autoimmune diseases. Moreover, repeated infections promote entry of *S. Pyogenes* specific T cells into the olfactory bulb and other CNS regions, whereas the bacteria remain within the nasal cavity. We also find microglial activation and barrier breakdown in close proximity to CNS-infiltrating T cells, as measured by leakage of both serum IgG and a low molecular weight tracer (biocytin-TMR), as well as disruption of endothelial cell tight junctions. These findings provide novel insight into how recurrent Streptococcus infections might impair brain function and lead to motor and neuropsychiatric diseases and suggest a general mechanism by which infectious agents that induce Th17 immunity might exacerbate other CNS autoimmune diseases such as multiple sclerosis to provoke long-term neurovascular damage.

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