Study suggests remarkable approach to MS treatment

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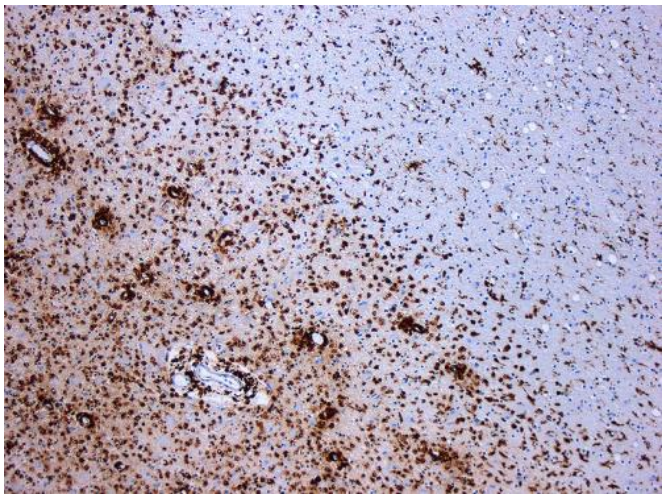

Demyelination by MS. The CD68 colored tissue shows several macrophages in the area of the lesion. Original scale 1:100. Credit: Marvin 101/Wikipedia

(Medical Xpress)—Multiple sclerosis (MS) is an autoimmune inflammatory disorder in which the immune system attacks the myelin sheath enveloping and insulating the nerves. A progressive disease that often results in severe neurological disabilities, it is also characterized by acute attacks in which sufferers experience such symptoms as partial paralysis, loss of feeling in the extremities, optic neuritis, memory problems, and problems with speech and swallowing.

Current treatments for MS focus on disease management, particularly interferon-based therapies that ameliorate the frequency of acute attacks, but do not halt disease progression. Additionally, interferon has unusually harsh side effects in the majority of patients, comparable in severity to those experienced by chemotherapy patients. The search for more effective and less toxic treatments for MS is thus a high priority for medical researchers and medical funding organizations.

Recently, a group of researchers at the Stanford Department of Neurology and Neurological Sciences explored the use of a synthetic bile acid agonist in a mouse model of multiple sclerosis with remarkable results. They've published their results in the *Proceedings of the National Academy of Sciences*.

Farnesoid X receptor (FXR) is a nuclear hormone receptor that interacts with bile acid synthesis, transport, and cholesterol metabolism. Recent studies indicate that bile acid-FXR regulation plays an important role in hepatic and intestinal inflammation. Notably, FXR-knockout mice have been observed to express higher disease severity in a mouse model of multiple sclerosis called experimental autoimmune encephalitis (EAE).

The researchers treated mice exhibiting EAE with an oral drug called obeticholic acid (6-ECDCA), a synthetic FXR agonist that is currently in clinical trials for the treatment of a number of inflammatory diseases. They also tested the mice with a natural FXR ligand (CDCA); in both cases, the disease was significantly ameliorated. They also found that 6-ECDA was more effective than the natural ligand at suppressing the disease.

The researchers were particularly surprised to find that oral administration of 6-ECDCAwas much more effective at ameliorating the disease that intraperitioneal injection. "The oral activity of obeticholic acid suggests further modulation of the drug by gut flora or gut enzymes or the importance of hepatic uptake," the authors write. Given that existing interferon treatments for MS patients involve regular, painful intramuscular injections, this is a discovery that holds significant promise not only to alleviate the suffering caused by MS, but also that caused by the daily or weekly self-administration of interferon and its attendant side effects.

Nonetheless, human patients receiving experimental 6-ECDCA therapy have been observed to exhibit side effects. Concerns about long-term safety arose when 23 percent of patients in a separate study's trial group developed severe skin itching and unexpected increases in total cholesterol and LDL cholesterol. The authors note that changes in serum cholesterol and insulin resistance confer an increased risk of development of atherosclerosis. They write, "One possibility may be to combine a statin with 6-ECDCA. Nevertheless, our data provide a previously unidentified approach in treating MS through the bile acid-FXR interaction."

More information: Obeticholic acid, a synthetic bile acid agonist of the farnesoid X receptor, attenuates experimental autoimmune encephalomyelitis. *PNAS* 2016 ; published ahead of print January 25, 2016, DOI: 10.1073/pnas.1524890113

Abstract
Bile acids are ligands for the nuclear hormone receptor, farnesoid X receptor (FXR). The bile acid–FXR interaction regulates bile acid synthesis, transport, and cholesterol metabolism. Recently, bile acid–FXR regulation has been reported to play an integral role in both hepatic and intestinal inflammation, and in atherosclerosis. In this study, we found that FXR knockout mice had more disease severity in experimental autoimmune encephalomyelitis (EAE), an animal model of multiple sclerosis (MS). Obeticholic acid (6?-ethyl-chenodeoxycholic acid, 6-ECDCA), a synthetic FXR agonist, is an orally available drug that is currently in clinical trials for the treatment of inflammatory diseases such as alcoholic hepatitis, nonalcoholic steatohepatitis, and primary biliary cirrhosis. When we treated mice exhibiting established EAE with 6-ECDCA, or the natural FXR ligand chenodeoxycholic acid (CDCA), clinical disease was ameliorated by (i) suppressing lymphocyte activation and proinflammatory cytokine production; (ii) reducing CD4+ T cells and CD19+ B cell populations and their expression of negative checkpoint regulators programmed cell death protein 1 (PD1), programmed death-ligand 1 (PD-L1), and B and T lymphocyte attenuator (BTLA); (iii) increasing CD8+ T cells and PD1, PDl-1, and BTLA expression; and (iv) reducing VLA-4 expression in both the T- and B-cell populations. Moreover, adoptive transfer of 6-ECDCA– or CDCA-treated donor cells failed to transfer disease in naive recipients. Thus, we show that FXR functions as a negative regulator in neuroinflammation and we highlight that FXR agonists represent a potential previously unidentified therapy for MS.