The neural androgen receptor: a therapeutic target for myelin regeneration

Men are less likely to develop multiple sclerosis than women, but they often have a more severe disease course and they reach disability milestones earlier. These observations have spurred interest in the potential immunomodulatory, anti-inflammatory and neuroprotective actions of testosterone. We have shown that testosterone therapy also promotes regeneration of the myelin sheaths, which is part of a natural healing process named "remyelination". Moreover, we have identified the neural androgen receptor (AR) as a novel therapeutic target for myelin recovery.

Testosterone stimulates the formation of new myelin sheaths in chronic demyelinated brain lesions resulting from cuprizone intoxication. In this model, spontaneous myelin regeneration no longer takes place, and it thus mimics the failure of remyelination in chronic multiple sclerosis lesions. However, testosterone failed to stimulate the formation of new myelin after specific knockout of the AR in neurons and macroglial cells. The potent synthetic testosterone analogue 7alpha-methyl-19-nortestosterone (MENT), which has been developed for long-term male contraception and androgen replacement therapy in hypogonadal men and does not stimulate prostate growth, also efficiently promoted myelin repair. A key role of AR-dependent testosterone signaling in myelin regeneration was also demonstrated in a model of acute and reversible demyelination caused by the stereotaxic infusion of lysophosphatidylcholine into the ventrolateral funiculus of the male mouse spinal cord. Spontaneous myelin regeneration was only observed in the presence of AR and functional testes or treatment with androgens. These results reveal an unexpected importance of AR signaling in the endogenous regeneration of myelin, and they qualify the AR as a promising drug target for promoting myelin repair.

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