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Androgenic hormones could help treat multiple sclerosis

Testosterone and its derivatives could constitute an efficient treatment against myelin diseases such as multiple sclerosis, reveals a study by researchers from the Laboratoire d'Imagerie et de Neurosciences Cognitives [1] (CNRS/Université de Strasbourg), in collaboration in particular with the "Neuroprotection et Neurorégénération: Molécules Neuroactives de Petite Taille" unit (Inserm/Université Paris-Sud)[2]. Myelin composes the sheaths that protect the nerve fibers and allow the speed of nerve impulses to be increased. A deficit in the production of myelin or its destruction cause serious illnesses for which there is no curative treatment. The researchers have shown that in mice brains whose nerve fibers have been demyelinated, testosterone and a synthetic analog induce the regeneration of oligodendrocytes, the cells responsible for myelination, and that they stimulate remyelination. This work is published on January in the journal *Brain*.

Multiple sclerosis (MS) is a degenerative disease of myelin, which is accompanied by severe inflammation of the central nervous system. Affecting around 80,000 people in France, it is characterized by motor and vision disorders and by neurological impairments such as elocution difficulties. MS is also known to have a hormonal component. In fact, women are twice as susceptible as men, even though the prognosis is less good for males. In addition, it has been observed that pregnant women suffering from MS do better during pregnancy when their hormone levels are high. The team headed by Dr Said Ghandour had already demonstrated the protective effect of testosterone on oligodendrocytes (the cells responsible for myelination).

For this study, the researchers firstly induced chronic demyelination of the nerve fibers in the brain of mice. To do this, they added cuprizone, a molecule that sequesters copper, to their diet. The mice then exhibited chronic demyelination, analogous to that observed during the progressive phase of MS. They were then treated with testosterone for 6 to 9 weeks. As a result, their nerve fibers were once again myelinated and their symptoms were remarkably alleviated. The same effects were obtained using a synthetic testosterone analogue, 7-alpha-methyl-19-nortestosterone (MENT).

The researchers then showed that these androgens bring about the transformation of neural stem cells into oligodendrocytes and promote the synthesis of myelin by oligodendrocytes, thus maintaining the integrity of the nerve fibers. They then repeated the experiment, but this time using two transgenic mouse strains: one with a mutated androgen receptor and the other with a receptor that had been selectively inactivated in the

[1] More precisely, the "Biopathologie et Imagerie de la Myeline" team within this laboratory.
[2] Other French laboratories also participated in this work to a lesser extent, in particular the "Physiopathologie et Psychopathologie Cognitive de la Schizophrénie" unit (Inserrm/Université de Strasbourg), the "Cellules Souches et Radiations" unit (Inserm/CEA/Universités Paris-Diderot and Paris-Sud), and the "Physiopathologie des Maladies du Système Nerveux Central" unit (CNRS/UPMC/Inserm).

central nervous system. In these androgen-insensitive mice, testosterone did not stimulate remyelination of the nerve fibers.

These results identify the androgen receptor as a promising therapeutic target for treating diseases such as MS. They open the way to the use of androgens—including that of testosterone analogues such as MENT, which is well tolerated in humans—to promote the regeneration of myelin. Further work will focus on the possibility of using testosterone blood levels as biomarkers to evaluate the progression of demyelinating diseases.

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Figure 1: Histological section of a control mouse brain. Myelin and myelinating cells (oligodendrocytes) have been made fluorescent using a gene encoding for a green fluorescent protein (GFP) in order to facilitate the identification and monitoring of the destruction of myelin and its repair.

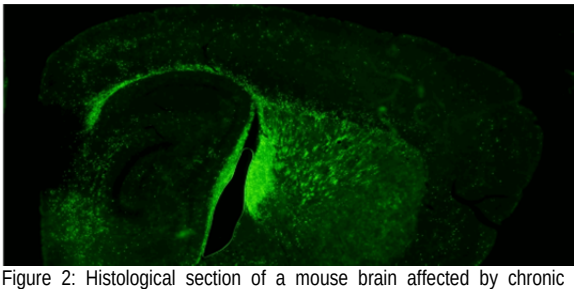

Figure 2: Histological section of a mouse brain affected by chronic demyelination. The intensity of the green fluorescence is considerably reduced. This is attributed to the destruction of myelin and to the cell death of a large number of oligodendrocytes.

Figure 3: Histological section of a mouse brain treated with testosterone for 6 weeks following severe demyelination such as that observed in figure 2. A significant recovery of oligodendrocytes and myelin is observed following this hormonal treatment.

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