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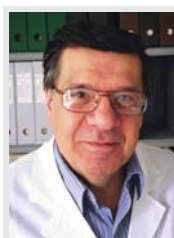
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The androgen receptor as a therapeutic target for myelin repair in demyelinating diseases

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Steroid hormones exert major influences on the development and functioning of the nervous system, extending well beyond their reproductive effects. There is now also strong experimental evidence for an important role of these hormones in myelin formation. The recent finding that testosterone, via the intracellular androgen receptor, promotes myelin repair, may inspire neurobiologists to take a closer look at this hormone. It also opens new therapeutic opportunities for androgen receptor ligands in the treatment of myelin disorders.

The demyelinating diseases cover many disorders of the nervous system in which myelin sheaths are destroyed. Myelin damage impairs signal conduction along axons and also leads to neuronal degeneration. The most common demyelinating disease is multiple sclerosis (MS), which affects between 2 and 3 million people worldwide, with rates varying widely between different regions and populations. While the causes of MS are still not well understood, this neurodegenerative disorder involves autoimmune and inflammatory destruction of myelin sheaths and the death of oligodendrocytes, which are the myelin producing cells of the CNS. These damages can generate a wide range of neurological problems, often leading to permanent disability in patients at advanced disease stages.

Current MS treatments successfully target the immune system and neuroinflammatory responses during relapses, but have no clear beneficial effect on the progression of disability [1]. Urgently needed are effective new treatments for promoting the remyelination of demyelinated axons, also referred to as myelin repair. In contrast to the limited regenerative ability of neurons, lost myelin can indeed be replaced within the adult

CNS by a process involving the proliferation, migration and differentiation of oligodendrocyte precursor cells (OPCs) into mature, myelin forming oligodendrocytes. However, although OPC are widely distributed throughout the adult CNS, the myelin repair remains very limited. Moreover, OPC may remain trapped in an undifferentiated state after myelin injury. Thus, an increasing interest exists for the identification of new pharmacological targets and the development of small molecule drugs stimulating endogenous myelin repair such as thyroid hormone [2], ligands of retinoid X receptors [3] and progestins [4]. Other recently identified potential targets for remyelination therapies are the Sonic Hedgehog [5] and Wnt/beta-catenin [6,7] signaling pathways.

A new and promising drug target for myelin repair has now joined this list: the androgen receptor (AR). This may come as a surprise, as testosterone is well known as a male sexual hormone, and as its actions have been considered as limited to reproduction. However, CNS is an important target of this hormone, and improved immunological methodologies have revealed the large distribution and abundance of AR throughout the brain [8]. Although several studies have

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addressed the cellular distribution of AR in the brain, they need to be revisited with appropriate and diverse probes for a comprehensive understanding of the neural cell-type-specific expression and regulation of the receptor. In the male rat fore-brain, AR has been localized mainly in neurons and in some astrocytes, and they were shown to be strongly up-regulated in microglial cells in response to injury [8]. Also, the presence of AR has been demonstrated in astrocytes and oligodendrocytes in the prefrontal cortex of adult rhesus monkeys [9].

Androgens can thus be expected to have multiple functions in the CNS, and their neuroprotective effects have been documented in some experimental models [10,11]. In addition, testosterone exerts immunomodulatory effects and acts directly on T lymphocytes [11]. Beneficial neuroprotective and immunosuppressive actions of testosterone have also been documented in experimental autoimmune encephalomyelitis (EAE), a widely used animal model of MS [12]. Testosterone treatment ameliorates EAE signs in both female and male mice and its protective effect was shown to be mediated through AR since 5 α DHT treatment was effective [12,13] and beneficial effects were reversed with flutamide [14]. These experimental studies provided the support for a clinical trial, in which the effects of testosterone supplementation were studied in men with relapsing-remitting MS during one year. Major outcomes were the safety of the treatment, improved cognitive performance, reduced brain atrophy and anti-inflammatory effects [15,16]. The effect of testosterone on cognition was further explored recently in EAE [17]. Testosterone treatment decreased hippocampal pathology by reducing microglial activation, restoring synaptic protein expression and improving synaptic transmission [17].

That testosterone may play a role in myelination was suggested by several observations. First, the number of oligodendrocytes in white matter tracts of the rodent CNS is greater in males compared with females. Moreover, long-term castration of adult male rats significantly reduces the number of oligodendrocytes, which become comparable to the one observed in females [18]. Another study has reported that the growth of white matter during human adolescence shows a striking sexual dimorphism, assessed by T1-weighted images and magnetization transfer ratio on brain MRI. During puberty, the volume of white matter only slowly increases in girls, but sharply in boys. Evidence of the role of AR in the rapid white matter growth in boys was provided by studying a functional polymorphism in the AR gene, which determines the transcriptional activity of the receptor and affects the increase in white-matter volume. However, testosterone was proposed to affect the caliber of myelinated axons rather than the thickness of the myelin sheaths [19].

In a recently reported study, Hussain *et al.* have shown that testosterone treatment very efficiently stimulates the generation of new oligodendrocytes and the formation of new myelin sheaths after induction of chronic demyelination in the mouse brain, analogous to that observed during the progressive phase of MS [20]. Testosterone was administered to castrated male mice to induce plasma and brain levels of the hormone in the normal nanomolar range. Interestingly, testosterone therapy

efficiently promoted myelin repair in both males and females. Examination of the brain sections from testosterone-treated mice demonstrated complete regeneration of the myelin sheaths within the corpus callosum, a large tract of myelinated fibers, which connects the left and right cerebral hemispheres. Importantly, testosterone also significantly increased the diameter of axons, suggesting additional neurotrophic effects. The study further revealed that testosterone stimulated the proliferation of OPC followed by their differentiation into mature oligodendrocytes [20].

Testosterone can exert its effects on target cells via multiple mechanisms, involving the intracellular AR, membrane sites of action and its conversion to neuroactive metabolites such as estradiol. The neural AR was then identified as a key target for the remyelinating effects of the hormone. In fact, testosterone treatment failed to promote myelin repair in testicular-feminized mice with a non-functional AR and, most important, after specific conditional ablation of the AR in neurons, oligodendrocytes and astrocytes, sparing microglia. Thus, a functional brain AR is required for the remyelination effect of testosterone [20]. The anti-inflammation effect of testosterone could be mediated by AR of the spared microglia. Furthermore, the role of each cell-type expressing AR in myelin repair needs to be thoroughly investigated.

The remyelination of axons was indeed efficiently stimulated by administration of the potent synthetic AR agonist 7 α -methyl-19-nortestosterone (MENT), which has been developed for long-term male contraception and androgen replacement therapy in hypogonadal men [21]. Interestingly, MENT is not a substrate for the 5 α -reductase enzyme and thus does not stimulate growth of the prostate, a major concern with androgen therapy.

The identification of the brain AR as a promising therapeutic target for promoting myelin repair requires some cautious reflections. First, androgens have gained a bad reputation over the past years as different anabolic formulations are used at high doses for increasing the performance of athletes, with their well-known undesired side-effects. We are not proposing androgen treatments for exceeding physical limitations of the body, but for the normalization of androgen levels and actions for therapeutic purposes. There are indeed several reports of reduced testosterone levels in MS patients [22], and most recently lower testosterone levels correlated with higher disability scores (Expanded Disability Status Scale) at baseline, as well as with worse cognitive function scores (Symbol Digit Modalities Test) in the subsequent 2 years [23]. Second, the use of androgens is often associated with the fear of cancer, and in particular with prostate cancer. However, it has to be noted that deregulations of AR signaling or other intracellular signaling mechanisms are at the origin of prostate cancer. Moreover, long-term treatments with testosterone or synthetic androgens have been proven safe and well tolerated. Notably, the risk: benefit ratio of testosterone treatment in neurodegenerative diseases is quite different than that in healthy men. In addition, concerns with prostate health can be resolved by using synthetic analogues of testosterone, which spare the prostate such as

MENT. Finally, the normalization of testosterone levels or the administration of synthetic androgens may also be beneficial for women with MS, although at low doses. Indeed, testosterone is also a very important endogenous hormone in women, and testosterone insufficiency in women has been related to many diseases [24].

In conclusion, we propose that natural or synthetic ligands of the AR offer new and promising opportunities for boosting the endogenous capacity of myelin repair in patients with demyelinating diseases. Long-term testosterone treatment has been proven safe, and outcomes of a first clinical trial in men with relapsing-remitting MS have been very encouraging. Moreover, testosterone and synthetic androgens have the

advantage of easily crossing the blood–brain barrier and of diffusing rapidly throughout nervous tissues. We hope that the recent identification of the neural AR as a promising drug target for remyelination strategies will spur further efforts in the field and provide the basis for new clinical trials.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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References

- Kieseier BC, Stuve O. A critical appraisal of treatment decisions in multiple sclerosis—old versus new. *Nat. Rev. Neurol.* 7, 255–262 (2011).
- Harsan LA, Steibel J, Zaremba A *et al.* Recovery from chronic demyelination by thyroid hormone therapy: myelinogenesis induction and assessment by diffusion tensor magnetic resonance imaging. *J. Neurosci.* 28, 14189–14201 (2008).
- Huang JK, Jarjour AA, Nait OB *et al.* Retinoid X receptor gamma signaling accelerates CNS remyelination. *Nat. Neurosci.* 14, 45–53 (2011).
- Hussain R, el-Etr M, Gaci O *et al.* Progesterone and nestorone facilitate axon remyelination: a role for progesterone receptors. *Endocrinology* 152, 3820–3831 (2011).
- Ferent J, Zimmer C, Durbec P, Ruat M, Traiffort E. Sonic Hedgehog signaling is a positive oligodendrocyte regulator during demyelination. *J. Neurosci.* 33, 1759–1772 (2013).
- Fancy SP, Baranzini SE, Zhao C *et al.* Dysregulation of the Wnt pathway inhibits timely myelination and remyelination in the mammalian CNS. *Genes Dev.* 23, 1571–1585 (2009).
- Tawk M, Makoukji J, Belle M *et al.* Wnt/β-catenin signaling is an essential and direct driver of myelin gene expression and myelinogenesis. *J. Neurosci.* 31, 3729–3742 (2011).
- DonCarlos LL, Sarkey S, Lorenz B *et al.* Novel cellular phenotypes and subcellular sites for androgen action in the forebrain. *Neuroscience* 138, 801–807 (2006).
- Finley SK, Kritzer MF. Immunoreactivity for intracellular androgen receptors in identified subpopulations of neurons, astrocytes and oligodendrocytes in primate prefrontal cortex. *J. Neurobiol.* 40, 446–457 (1999).
- Fargo KN, Foecking EM, Jones KJ, Sengelaub DR. Neuroprotective actions of androgens on motoneurons. *Front. Neuroendocrinol.* 30, 130–141 (2009).
- Liva SM, Voskuhl RR. Testosterone acts directly on CD4+ T lymphocytes to increase IL-10 production. *J. Immunol.* 167, 2060–2067 (2001).
- Palaszynski KM, Loo KK, Ashouri JF, Liu HB, Voskuhl RR. Androgens are protective in experimental autoimmune encephalomyelitis: implications for multiple sclerosis. *J. Neuroimmunol.* 146, 144–152 (2004).
- Dalal M, Kim S, Voskuhl RR. Testosterone therapy ameliorates experimental autoimmune encephalomyelitis and induces a T helper 2 bias in the autoantigen-specific T lymphocyte response. *J. Immunol.* 159, 3–6 (1997).
- Matejuk A, Hopke C, Vandenbark AA, Hurn PD, Offner H. Middle-age male mice have increased severity of experimental autoimmune encephalomyelitis and are unresponsive to testosterone therapy. *J. Immunol.* 174, 2387–2395 (2005).
- Sicotte NL, Giesser BS, Tandon V *et al.* Testosterone treatment in multiple sclerosis: a pilot study. *Arch. Neurol.* 64, 683–688 (2007).
- Gold SM, Chalifoux S, Giesser BS, Voskuhl RR. Immune modulation and increased neurotrophic factor production in multiple sclerosis patients treated with testosterone. *J. Neuroinflammation* 5, 32 (2008).
- Ziehn MO, Avedisian AA, Dervin SM, Umeda EA, O'Dell TJ, Voskuhl RR. Therapeutic testosterone administration preserves excitatory synaptic transmission in the hippocampus during autoimmune demyelinating disease. *J. Neurosci.* 32, 12312–12324 (2012).
- Cerghet M, Skoff RP, Bessert D, Zhang Z, Mullins C, Ghandour MS. Proliferation and death of oligodendrocytes and myelin proteins are differentially regulated in male and female rodents. *J. Neurosci.* 26, 1439–1447 (2006).
- Perrin JS, Herve PY, Leonard G *et al.* Growth of white matter in the adolescent brain: role of testosterone and androgen receptor. *J. Neurosci.* 28, 9519–9524 (2008).
- Hussain R, Ghoumari AM, Bielecki B *et al.* The neural androgen receptor: a therapeutic target for myelin repair in chronic demyelination. *Brain* 136, 132–146 (2013).
- Nieschlag E, Kumar N, Sitruk-Ware R. 7α-Methyl-19-nortestosterone (MENT (R)): the Population Council's contribution to research on male contraception and treatment of hypogonadism. *Contraception* 87, 288–295 (2013).
- Wei T, Lightman SL. The neuroendocrine axis in patients with multiple sclerosis. *Brain* 120, 1067–1076 (1997).
- Bove R, Musallam A, Healy BC *et al.* Testosterone and disease severity in men with early relapsing onset multiple sclerosis. *Am. Acad. Neurol. Abstracts* (2013).
- Haring R, Hannemann A, John U *et al.* Age-specific reference ranges for serum testosterone and androstenedione concentrations in women measured by liquid chromatography-tandem mass spectrometry. *J. Clin. Endocrinol. Metab.* 97, 408–415 (2012).