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Commentary

Nerve growth factor as a new treatment for testosterone deficiency?

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As a clinician and researcher in the treatment of male infertility and sexual dysfunction, I was intrigued by the work of Luo and co-workers in this volume of EBioMedicine [1]. The authors investigated the effect of intranasal administration of nerve growth factor (NGF) in aging male mice, and reported a variety of benefits, including enhanced sexual function, improved sperm quality, and restored fertility in SAMP8 mice. Experiments suggest these multiple effects were mediated via gonadotropin-releasing hormone (GnRH) release through the PKC/p-ERK1/2/p-CREB signal pathway. What is the clinical significance of this work?

To provide similar results in humans would be a major accomplishment. Infertility affects approximately 15% of US couples, and reduced sperm parameters are found in approximately half of these [2]. Testosterone deficiency (also called hypogonadism) is noted biochemically in as many as 35% of men over 45 years [3], and presents with a number of clinical manifestations, including decreased libido, erectile dysfunction, chronic fatigue, muscle loss, increased fat mass, anemia, and decreased bone density [4].

Standard treatment for testosterone deficiency is exogenous testosterone, administered via injections, subcutaneous pellets, topical treatments, and nasal gels. While these treatments effectively raise serum testosterone and alleviate symptoms, the negative feedback exerted by exogenous testosterone on the hypothalamic-pituitary-gonadal (HPG) axis results in suppressed secretion of the pituitary gonadotropins, luteinizing hormone (LH) and follicle stimulating hormone (FSH), which in turn results in testicular atrophy and severe reductions in sperm production, often to complete azoospermia. Whereas older men with testosterone deficiency may not be concerned about infertility and reduced testicular volume as long as their sexual symptoms are improved, infertility and reduced testicular volume can be a troublesome adverse effect for younger and middle-aged men.

A reasonable treatment alternative that preserves or even improves fertility and testicular volume is administration of human chorionic gonadotropin (hCG) [5], which mimics the actions of LH, directly stimulating the Leydig cells of the testis to produce more testosterone. However, its clinical acceptability is limited by the requirement for frequent subcutaneous injections, usually 2–3 times per week, due to its relatively short half-life. The use of hCG for management of testosterone deficiency is limited to men with hypogonadotropic hypogonadism, which accounts for approximately 80% of hypogonadism cases. The remaining 20% have some abnormality or absence of the testicles, associated with elevated LH and/or FSH levels.

The authors here provide a possible new avenue for treatment of testosterone deficiency, namely the use of NGF, delivered intranasally. Their experimental data convincingly show that GnRH is stimulated, which in turn stimulates LH secretion and increased testosterone production. Whereas pulsatile GnRH treatment has been shown to be effective in men with hypogonadotropic hypogonadism, by modifying GnRH secretion itself, NGF may provide an even more direct, "natural" treatment. This interesting approach would modify testosterone secretion at the earliest step, leaving intact all downstream systems to function via their usual physiological mechanisms.

To date, nasal treatment of testosterone deficiency appears limited to a concentrated testosterone gel [6]. Experience is still limited with this relatively new product, with advantages being convenience, lack of transference of testosterone to women and children, and rapid onset. Challenges include unfamiliarity with nasal administration of medication and the need for 2–3 administrations per day.

The authors speculate that aging males in their mouse model demonstrate testosterone deficiency due to a deficiency in NGF signaling in the brain. It is difficult to know whether a similar mechanism may apply in humans. The key question from this work is whether the results are specific to this mouse strain. If similar results can be obtained in other strains or species, these results may open up a fertile (pun intended) new line of investigation.

The vast majority of cases of testosterone deficiency in men occur without a known underlying etiology, and these cases are often termed "age-related hypogonadism." However, this is a term is without much meaning, since most medical conditions in humans (examples: hypertension, diabetes, coronary artery disease, cancer, arthritis) are age-related, indicating only that they become more prevalent with advancing age. Yet this tells us nothing about the biochemical or biological mechanisms contributing to a deficiency of testosterone. It is plausible that a deficiency of a message such as NGF could be one mechanism that contributes to age-related hypogonadism.

The value of understanding the mechanism of disease is that ideally one may arrive at an elegant treatment that directly addresses the underlying etiology. Increased specificity of treatment should in theory provide a more acceptable risk profile for such treatment. I look forward to continued work on the relationship of NGF to male infertility and testosterone deficiency, and perhaps one day, to its clinical applicability of NGF as a therapeutic treatment.

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Conflict of interest

The authors declare no conflicts of interest.

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