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Trazodone associated with Clomiphene a proposal treatment for post finasteride syndrome

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Abstract

Erectile dysfunction caused by medications are probably caused by the disconnection of synaptic circuits responsible for linking libido to erection. For instance, it is well known that sexual dysfunction may occur in patients treated with finasteride, an inhibitor of the enzyme 5alpha-reductase, prescribed for androgenetic alopecia and benign prostatic hyperplasia. Interestingly, sexual dysfunction persists after drug discontinuation. Clomiphene citrate is a selective estrogen receptor modulator that has been used for the treatment of hypogonadism in men. It acts centrally to increase secretion of luteinizing hormone. Trazodone is a multifunctional drug with hypnotic actions at low doses due to blockade of 5-HT2A receptors, as well as H1 histamine receptors and α1 adrenergic receptors, therefore this drug can cause severe priapism and in many cases causing penile necrosis or permanent loss of erectile function. Therefore, we propose that trazodone and clomiphene can restore libido synaptic circuits, thus these associated drugs can be a treatment for post-finasteride syndrome.

Keywords: Trazodone treatment; Clomiphene treatment; Post finasteride syndrome; Epigenetic mechanism

1. Introduction

The post-finasteride syndrome is not directly associated with a decrease in androgen levels or testosterone [1, 2]. But, finasteride can affect, the levels of 5alpha-reduced metabolites of progesterone and testosterone, as the further metabolites and precursors suggesting that this drug has broad consequence on neuroactive steroid levels of post-finasteride syndrome (PFS) patients [3].

Theoretically the drugs trazodone, clomiphene and finasteride would have an epigenetic action mechanism in the brain. But both drugs clomiphene and trazodone have an epigenetic action opposed to finasteride. So, a proposal action mechanism of finasteride inside neuron, could be an imbalance in the messenger RNA of androgen receptors [4 ,5, 6].

Thus, finasteride causes a decrease of dihydrotestosterone (DHT) in the brain by inhibition of the 5alpha-reductase enzyme, and consequently an increase in the level of free testosterone. So, this hormonal imbalance could also cause an epigenetic change in histone methylation, inhibiting neuronal expression of testosterone receptors [6].

Clomiphene may change the hypothalamus-pituitary-gonad axis (Figure1) and result in the alteration of the testosterone and estrogen ratio [7]. Clomiphene citrate is a non-steroid agent, with anti-estrogenic properties, which can induce ovulation in certain women who do not ovulate [8]. Thus, clomiphene acts by inhibiting the estrogen negative feedback mechanisms in hypothalamic-pituitary-gonadal axis [8].

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Its action mechanism competing with endogenous estrogen in hypothalamic estrogen receptors (Figure 1). In this way, it inhibits the retro negative feeding of steroid hormones [9], inducing an ovulatory response in women and increased testosterone in men; through increased production of pituitary gonadotropins, increased GnRH secretion (gonadotropin release hormone), LH (luteinizing hormone) and FSH (follicle stimulating hormone) levels, which results in ovarian and testicular stimulation [8, 9].

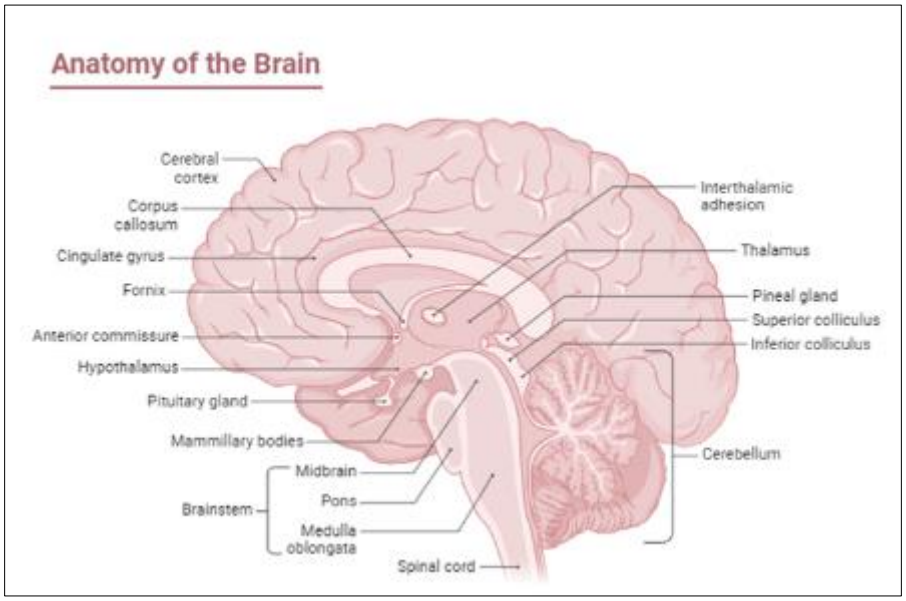

Figure 1 There is a relationship between dihydrotastosterone (DHT) and free testosterone in the normal brain. Finasteride causes an imbalance in the relationship between dihydrotastosterone (DHT) and testosterone in many brain structures, causing an epigenetic change in different regions of the central nervous system. Created with BioRender.com.

But, increased endogenous testosterone also causes a secondary increase in the estrogen due to the performance of the aromatase [10]. Which in men, with post finasteride syndrome, can increase the risk of a negative feedback rebound effect caused by estrogen.

Trazodone is amultifunctional drug with hypnotic actions at low doses due to blockade of 5-HT2A receptors, as well as H1 histamine receptors and α1 adrenergic receptors therefore this drug can cause severe priaprism as a side effect and in many cases causing penile necrosis or permanent loss of erectile function [11].

Like this, certain drugs such as trazodone and clomiphene citrate could in theory reverse the symptoms of finasteride [6, 11]. It is possible that inside neurons the trazodone, by some signaling pathway, cause acetylation of histones in genes responsible for the response to testosterone. This acetylation would increase the transcription rate of cortex neuronal androgen receptors (Figure 1). So, in normal patients, the response to the testosterone and libido would increase, including nocturnal erection and the risk of priapism [6, 11].

Thus, in post finasteride syndrome, the patient's age [12] as length of use finasteride or dutasteride are considerable factors in the severity of side effects [13].

However, clomiphene citrate and tamoxifen are chemical compounds that affect vision. Tamoxifen would have a similar action to clomiphene, but its side effects on vision are even more severe [14].

2. Conclusion

Post finasteride syndrome is not characterized by a decrease in androgen levels. However, even with normal testosterone levels, patients complain loss of libido and loss of brain-penis connection. This type of desensitization may be due to changes in the neurons of the cerebral cortex, which would respond to the motor sensation of libido.

Trazodone probably acts in the cortex and hypothalamus, while clomiphene acts in deeper structures such as the hypothalamus, causing a synergistic effect, to restoring brain sensitivity to the effects of testosterone and its metabolites.

Therefore, the use of clomiphene associated with trazodone could reverse severe cases of post-finasteid syndrome.

Compliance with ethical standards

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References

[1] Traish AM. Post-finasteride syndrome: a surmountable challenge for clinicians. Fertil Steril. 2020; 113(1):21-50.

[2] Giatti S, Diviccaro S, Panzica G, Melcangi RC. Post-finasteride syndrome and post-SSRI sexual dysfunction: two sides of the same coin? Endocrine. 2018; 61(2):180-93.

[3] Melcangi RC, Santi D, Spezzano R, Grimoldi M, Tabacchi T, Fusco ML, et al. Neuroactive steroid levels and psychiatric and andrological features in post-finasteride patients. J Steroid Biochem Mol Biol. 2017; 171:229-35.

[4] Davey RA, Grossmann M. Androgen Receptor Structure, Function and Biology: From Bench to Bedside. Clin Biochem Rev. 2016; 37(1):3-15.

[5] Melcangi RC, Casarini L, Marino M, Santi D, Sperduti S, Giatti S, et al. Altered methylation pattern of the SRD5A2 gene in the cerebrospinal fluid of post-finasteride patients: a pilot study. Endocr Connect. 2019;8(8):1118-25.

[6] Eric Almeida Xavie. Trazodone by epigenetic mechanism can reverse the post finasteride syndrome. Magna Scientia Advanced Research and Reviews. 2023; 09(02), 047–050.

[7] Liao Y, Chang YK, Wang SM, Chang HC. Ceiling effect of clomiphene citrate on the testosterone to estradiol ratio in eugonadal infertile men. PLoS One. 2022; 17(1):e0262924.

[8] Dorota J. Hawksworth, Arthur L. Burnett. Effects of Lifestyle on Men's Health. Chapter 4.2. (ISBN: 978-0-12-816665-9). United States. Elsevier; 2019.

[9] Habous M, Giona S, Tealab A, Aziz M, Williamson B, Nassar M, et al. Clomiphene citrate and human chorionic gonadotropin are both effective in restoring testosterone in hypogonadism: a short-course randomized study. BJU Int. 2018; 122(5):889-97.

[10] Pelusi C, Fanelli F, Baccini M, De Pergola G, Triggiani V, Mezzullo M, et al. Impact of Clomiphene Citrate on the Steroid Profile in Dysmetabolic Men with Low Testosterone Levels. Horm Metab Res. 2021; 53(8):520-8.

[11] Eric Almeida Xavier. Trazodone and chlorpromazine a proposal treatment for syndrome post-finasteride and syndrome of post-selective serotonin reuptake inhibitors (post-SSRI). World Journal of Biology Pharmacy and Health Sciences. 2023; 15(01), 075–080

[12] Eric Almeida Xavier. The macromolecular machinery of the nucleus in the senescence process. World Journal of Advanced Research and Reviews. 2022; 15(02), 393–404.

[13] Fertig RM, Gamret AC, Darwin E, Gaudi S. Sexual side effects of 5-α-reductase inhibitors finasteride and dutasteride: A comprehensive review. Dermatol Online J. 2017; 23(11).

[14] Arora S, Surakiatchanukul T, Arora T, Errera MH, Agrawal H, Lupidi M, et al. Retinal toxicities of systemic anticancer drugs. Surv Ophthalmol. 2022; 67(1):97-148.