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Trazodone by epigenetic mechanism can reverse the post finasteride syndrome

Eric Almeida Xavier *

Department of biochemistry institute of chemistry, University of São Paulo, Av. Prof. Lineu Prestes, 748, Sao Paulo, 05508-900, Brazil.

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Abstract

The action mechanism of finasteride as inhibitor of the 5alpha-reductase enzyme in the brain could cause an epigenetic change imbalance in the messenger RNA of androgen receptor. The decrease of dihydrotestosterone (DHT) followed by an increase of free testosterone in the brain could in theory cause an imbalance in acetylation and methylation of histones in neurons. So, the post finasteride syndrome would be caused by an epigenetic change in androgen receptors of neurons circuits. Thus, the alpha-adrenergic antagonist properties of trazodone, for example cause priapism, and could change the epigenetic expression of androgen receptors in neuronal circuits responsible for erection and libido. Therefore, through this mechanism, the trazodone could reverse the effect of finasteride on the brain.

Keywords: Trazodone treatment; Post finasteride syndrome; Epigenetic mechanism

1. Introduction

Theoretically both drugs trazodone and finasteride would have an epigenetic action mechanism in the brain. But the trazodone epigenetic action would be opposed to finasteride.

Many drugs may induce sexual dysfunction during the treatment like, finasteride an inhibitor of the enzyme 5alpha-reductase (5α-R) used at 1 milligram dose to treatment of androgenetic alopecia (AGA) and at 5 milligram dose to treatment of benign prostatic hyperplasia (BPH).

Finasteride is an inhibitor of 5α-R type 1 and 2, although it has higher affinity for the type 2 in humans [1, 2]. This drug proved to be highly effective in the control of dihydrotestosterone (DHT) levels and the progression of (BPH). Thus, the dutasteride is mainly used for the treatment of PBH, for inhibiting both 5α-R type 1 and 2 with greater potency than finasteride [3], showing great efficacy against BPH symptoms.

Finasteride at a dosage of 5 milligrams used for prostatic hyperplasia has effects on libido and sexual potency as well as dudasteride. Thereby, finasteride has a long half-life even at a dosage of 1 milligram.

Thus, the side effects on sexual function can also occur due to progressive accumulation of the medication in the body [4]. Like this, several clinical studies showed sexual adverse effects during finasteride or dutasteride treatment, such as erectile and ejaculatory dysfunction and loss of libido [2, 5]. And persistent sexual side effects, like for instance feeling a lack of connection between the brain and penis, loss of libido and sex drive, difficulty in achieving an erection, genital numbness or paresthesia, even after discontinuation of the treatment [2, 4, 6, 7].

So, we found that many symptoms are due to an imbalance in neuronal factors, because other symptoms reported by patients with post finasteride syndrome (PFS) are reduction in self-confidence, decreased initiative and difficulty in

* Corresponding author: Eric Almeida xaviera ORCID iD 0000-0002-6751-1281

concentration, forgetfulness or loss of short-term memory, irritability, suicidal thoughts, anxiety, panic attack, and sleep problems [6, 7].

2. Discussion

A proposal action mechanism of finasteride inside neuron could be by imbalance in the messenger RNA of androgen receptors [8]. The decrease of dihydrotestosterone (DHT) in the brain caused by inhibition of the 5alpha-reductase enzyme cause an increase in free testosterone. So, this hormonal imbalance could also cause an epigenetic change in histone methylation, inhibiting neuronal expression of testosterone receptors [8].

The (Figure 1A) represented the relationship between dihydrotestosterone (DHT) and free testosterone in normal brain when, androgen receptors are in equilibrium. Thus, due to the effect of finasteride to inhibit 5alpha-reductase, testosterone is not converted into dihydrotestosterone, causing an accumulation of free testosterone in the brain (Figure 1B).

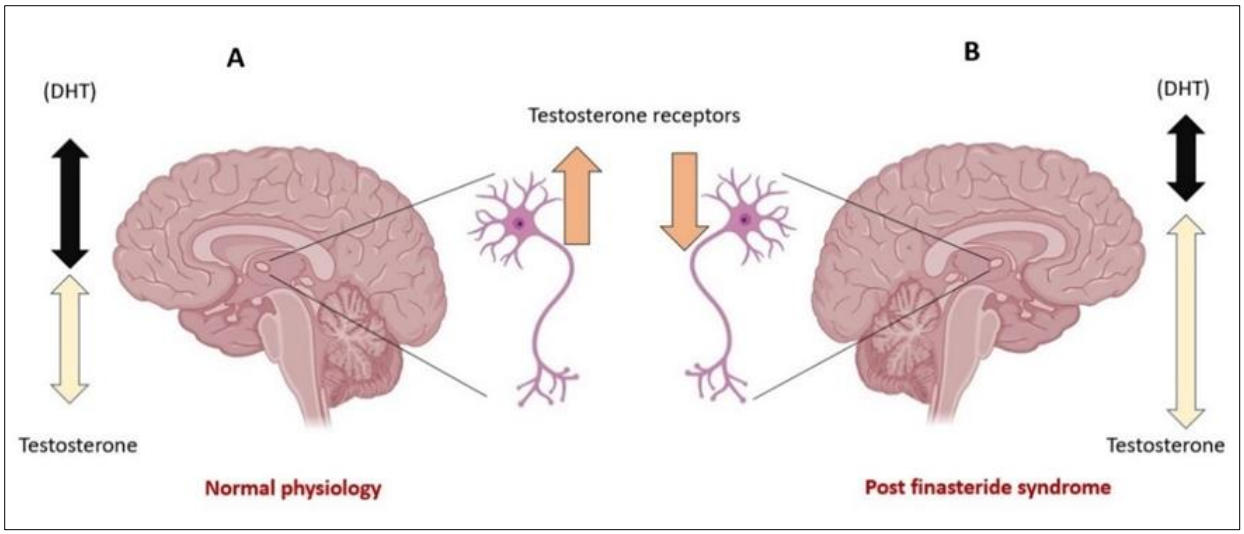

Figure 1 In (A) is represented the relationship between dihydrotestosterone (DHT) and free testosterone in normal brain. In (B) is represented the imbalance in post finasteride brain. Created with BioRender.com

In this way, hormone receptor of neurons circuits would self-regulate by balancing DHT versus testosterone, and excess of free testosterone associated with low levels of DTH would cause an epigenetic imbalance in the expression of androgen receptors. This resolution is made by the pattern of acetylation and methylation of histones, in receptor neurons at specific regions of the brain, such as the hypothalamus [8].

Certain drugs such as trazodone could in theory reverse the symptoms of finasteride [8]. 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 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 priaprism [8].

Thus, in patients with post finasteride syndrome the alpha-adrenergic antagonist properties of trazodone, by someway could change the epigenetic expression of receptors circuits responsible for erection and libido, causing a reversal effect of finasteride in the brain (Figure 2A).

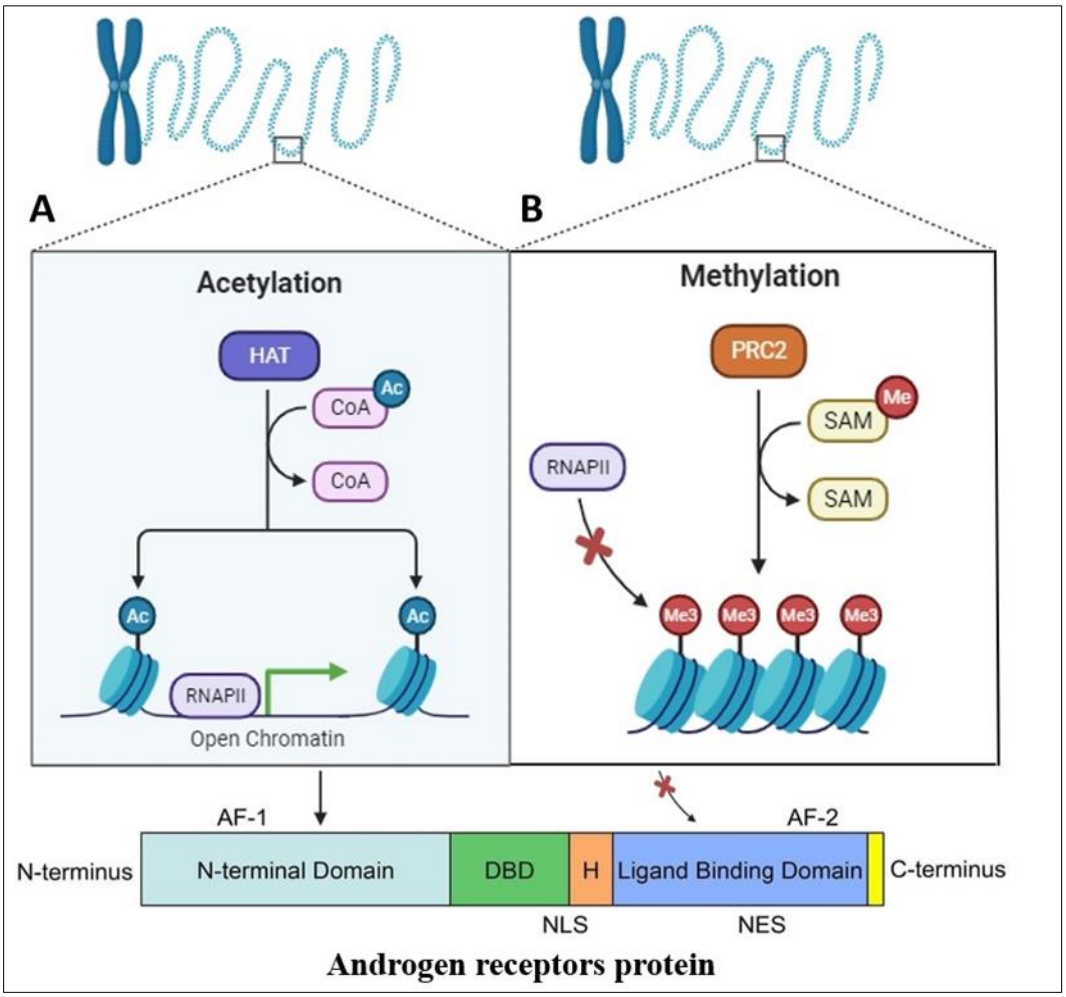

Figure 2 Histone methylation and acetylation mechanism. the acetylation of histones exposes the genetic material for transcription, after transcription the messenger RNA is translated into protein. For example, the androgen receptor. Created with BioRender.com

It is important to keep in mind that inside a cell, signaling cascades involve the interaction of different types of proteins. Thus, we suggest that an increase in the levels of transcription, or processing of the androgen receptor primary transcript could be an effect of trazodone in neurons.

For example, in (Figure 2) we have a representation of the androgen receptor (AR) showing your N-terminus domain, where is located the transcriptional activating function 1 (AF-1) and DNA binding domain (DBD). Like this, in C-terminus domain is located the ligand binding domain, the hinge region (H), transcriptional activating function 2 (AF-2), nuclear localisation signal (NLS) and nuclear export signal (NES) (Figure 2) [9].

Therefore, in post finasteride syndrome, the patient's age [10] as length of use finasteride or dutasteride are considerable factors in the severity of side effects [11].

3. Conclusion

It is important to establish initial treatment for the side effects of finasteride and dutasteride. Thus, trazodone could be indicated as an initial treatment for collateral effects of both drugs.

The systemic effect of finasteride and dutasteride covers the central nervous system and peripheral tissues. Thus, the physical and emotional side effects of both drugs can last long after discontinuation of use. So, this contributes to the thesis of deep epigenetic regulation in neurons. Therefore, the epigenetic change caused by finasteride and dutasteride is the theoretical cause of post finasteride syndrome.

Compliance with ethical standards

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References

[1] Finn DA, Beadles-Bohling AS, Beckley EH, Ford MM, Gililland KR, Gorin-Meyer RE, et al. A new look at the 5alpha-reductase inhibitor finasteride. CNS Drug Rev. 2006, 12(1):53-76.

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

[3] Frye SV, Bramson HN, Hermann DJ, Lee FW, Sinhababu AK, Tian G. Discovery and development of GG745, a potent inhibitor of both isozymes of 5 alpha-reductase. Pharm Biotechnol. 1998, 11:393-422.

[4] Lee S, Lee YB, Choe SJ, Lee WS. Adverse Sexual Effects of Treatment with Finasteride or Dutasteride for Male Androgenetic Alopecia: A Systematic Review and Meta-analysis. Acta Derm Venereol. 2019, 99(1):12-7.

[5] Nickel JC, Fradet Y, Boake RC, Pommerville PJ, Perreault JP, Afridi SK, et al. Efficacy and safety of finasteride therapy for benign prostatic hyperplasia: results of a 2-year randomized controlled trial (the PROSPECT study). PROscar Safety Plus Efficacy Canadian Two year Study. CMAJ. 1996, 155(9):1251-9.

[6] Gur S, Kadowitz PJ, Hellstrom WJ. Effects of 5-alpha reductase inhibitors on erectile function, sexual desire and ejaculation. Expert Opin Drug Saf. 2013, 12(1):81-90.

[7] 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.

[8] 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

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

[10] 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.

[11] 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).