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REVIEW ARTICLE

Pathophysiological and Neuropharmacological Mechanisms Underlying the Therapeutical Effects of Tianeptine

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Abstract:

Background:

Tianeptine, a drug that enhances rather than inhibits serotonin uptake by platelets and serotonergic axons, is able to act as an antidepressant and/or anti-stress drug.

Methods:

The former effect should be attributed to its ability to reduce neural sympathetic over activity, whereas the latter to the interference by the drug to the hypothalamic stress cascade which includes corticotropin releasing factor + ACTH + cortisol secretion.

Conclusion:

This singular mechanism should be taken into account when the drug is prescribed as a therapeutic agent.

Key words : Tianeptine, Depression, Epinephrine, Norepinephrine, Stress, Corticotropin releasing factor.

1. INTRODUCTION

Circulating serotonin (5-HT) includes platelet 5-HT (p5-HT) plus plasma 5-HT (f5-HT) pools. The former is significantly reduced in major (endogenous) depression (ED) patients [1]; whereas it is raised in dysthymic depression [2]. In addition, f5-HT is elevated in patients affected by the uncoping stress syndrome because of platelet aggregability triggered by raised levels of epinephrine (E) [3]. With respect to this, it is a well-known fact that tianeptine, a drug that enhances rather than inhibits platelet 5-HT uptake, has proved to be an effective antidepressant agent [4 - 8].

With respect to the above, we demonstrated that tianeptine lowers plasma norepinephrine (NE) levels [9], which is raised in ED patients [1] and thus, minimizes neural sympathetic hyperactivity [10], responsible for this syndrome. Thus, according to the above, we will try to explain these controversial facts.

2. CENTRAL NERVOUS SYSTEM (CNS) + PERIPHERAL NEUROAUTONOMIC + NEUROENDOCRINE CIRCUITRIES UNDERLYING PHYSIOLOGICAL + NEUROPHYSIOLOGICAL ACTIVITIES

The A5(NE) pontine nucleus is responsible for neural sympathetic activity, whereas the C1(E) medullary nuclei are positively correlated with adrenal sympathetic activity, which excites the release of epinephrine. The crosstalk between both circuitries modulates its contribution to the physiological requirements. With respect to this, both circuitries often modulates its activities according with the above mentioned requirements. In addition, both sympathetic branches may

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act in association or dissociation according with the physiological and/or pathophysiological circumstances [11].

In addition to the above, serotonergic mechanisms cooperate with parasympathetic nuclei addressed to modulate neural and adrenal sympathetic activities [12]. Serotonin is released at both CNS and peripheral levels. The former depends on hypothalamic 5-HT neurons, whereas the latter is released from the enterochromaffin cells which are excited by parasympathetic nerves. Furthermore, taking into account that circulating 5-HT is stored into platelets, f5-HT is increased because of deficit uptake and/or platelet aggregation. Platelet aggregation depends on the epinephrine overflow [13 - 15] and from parasympathetic over-activity [16], which enhances circulating 5-HT by excitation of enterochromaffin cells [17, 18].

According to all the above, we might conclude that the assessment of p5-HT and f5-HT allows the possibility to obtain adequate information dealing with the autonomic nervous system status.

3. TIANEPTINE AND MODULATION OF THE NEUROENDOCRINE CASCADE

The neurophysiological and neuropharmacological effects triggered by tianeptine depend on its ability to enhance platelet uptake of 5-HT and to inhibit neural sympathetic branch [9, 10]. These effects result in the minimization of f5-HT and plasma NE levels [9]. These actions redound in significant neuroautonomic changes underlying therapeutic or iatrogenic effects which should be adequately discussed and evaluated.

4. TIANEPTINE AND UNCOPIING STRESS SYNDROME

This syndrome is underlain by cortico-adrenal hyperactivity which is triggered by the overflow of 5-HT at hypothalamic level [19, 20]. With respect to this, it is a well-known fact the ability of tianeptine to interfere with this disorder and its polysynaptic secondary effects [21 - 24].

5. TIANEPTINE AND NEURAL SYMPATHETIC OVERACTIVITY (DEPRESSION CIRCUITRY)

It has been demonstrated that tianeptine reduces plasma NE levels [9] which are significantly raised in patients affected by neural sympathetic hyperactivity as occurs in Crôhn's disease, rheumatoid arthritis, sleep apnea, endogenous depression and many others syndromes [10, 12]. These facts, in addition to the ability of the drug to act at both CNS and peripheral ANS levels, explains its therapeutic effects on diverse pathologies.

6. TIANEPTINE AND CORTICO-ADRENAL OVERACTIVITY (STRESS CIRCUITRY)

Considering that this physiological disorder depends on the hyperactivity of the Dorsal Raphe(5-HT) + C1(E) axis [10, 12] it would be easy to understand that interfering this axis by the action of tianeptine should result in the suppression of the stress circuitry. In addition, considering that hypothalamic 5-HT is an obliged link between the CNS and peripheral neuroautonomic circuitry, which includes the corticotropin releasing factor + ACTH + cortisol cascade, seems obvious the interference by tianeptine at this level, reinforcing its role as a powerful anti-stress drug modulating neuroendocrine and behavioral responses [19 - 24].

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest regarding the publication of this paper.

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