ORIGINAL ARTICLE

The Enygma of Asthenia: A Study of Angiotensin 1-7 and Melatonin in the Treatment of Asthenia Induced by Different Pathological Conditions

Paolo Lissoni[1], Giorgio Porro[1], Arianna Lissoni[1], Davide Porro[1], Franco Rovelli[1], Giulia Aliboni[1], Mauro Mantoani[1], Giuseppe Di Fede[1], Agnese Valentini[2], Massimo Colciago[3] Ana Cristina Simoes-e-Silva[4], Daniel Cardinali[5]

[1]Institute of Biological Medicine, Milan, Italy, [2]Madonna del Soccorso Hospital, San Benedetto del Tronto, Ascoli Piceno, Italy, [3]INRCA-IRCCS Institute, Casatenovo, Lecco, Italy, [4]Laboratorio interdisciplinar dei Investigacao Medica, Facultade de Medicina, Universitade Federal de Minas Gerais, Belo Horizonte, Brazil, [5]Pontificia Universitad Catolica Argentina, Buenos Aires, Argentina

ABSTRACT

Asthenia, which is defined as a subjective privation of force, may occur in all chronic inflammation-related diseases, and it would be due to alterations in neurotransmitter pathways induced by an abnormal production of inflammatory cytokines. Chronic disease-related enhanced production of inflammatory cytokines may be controlled by the pineal hormone melatonin (MLT) and angiotensin 1-7 (Ang 1-7), the active molecule produced by the action of ACE2, which is widely expressed by most tissue, including brain. Therefore, both MLT and Ang 1-7 could be effective in the treatment of asthenia. On these bases, a study was planned to evaluate the effects of a concomitant administration of high-dose MLT plus low-dose Ang 1-7 in patients suffering from asthenia due to different causes. The study included 72 consecutive patients with asthenia, which was due to advanced cancer in 23 patients, Covid19 infection in 17, post-Covid19 syndrome in 15, cardiopathy in 7, neurodegenerative pathologies in 4, multiple sclerosis in 3, and diabetes in the remaining 3 cases. MLT was given orally at 100 mg/day in the evening. Ang 1-7 was also given orally at 0.5 mg twice/day. Irrespectively of the pathology, a rapid relief of asthenia was achieved in 51/72 (71%) patients. Moreover, the relief of asthenia was associated with an improvement of the inflammatory status. In conclusion, this preliminary study shown that the neuroendocrine regimen of high-dose MLT in association with low-dose Ang 1-7 is an effective and well tolerated therapy of asthenia.

Key words: Angiotensin1-7, Asthenia, Inflammatory cytokines, Melatonin, Neuroimmunomodulation.

INTRODUCTION

Asthenia or fatigue is a symptom difficult to be defined because of the symptom of asthenia is often vague, and it may be influenced by several subjective variables, including sensation and affect. In any case, asthenia may be defined as a subjective privation of force and absence of energy (1,2). The advanced cancer is often characterized by the occurrence of important asthenia. If we exclude anaemia, depression and important cardiopathy, the neurochemical

Address for correspondence: Paolo Lissoni, Institute of Biological Medicine, Milan, Italy.

DOI: 10.33309/2639-8354.040102

mechanisms responsible for the asthenia are still understood, despite the recent great advances in the knowledge of the neurochemical mediation of the different psychological conditions. In fact, it is known that stress is mainly related to an enhanced catecholamine secretion, pain is controlled by the opioid system, mood is under a serotoninergic control, pleasure is mediated by dopamine, GABA-A and endogenous cannabinoids (3), sleep is promoted by the pineal hormone melatonin (MLT) (4), while no clear neurochemical mediation has been suggested to explain the occurrence of fatigue for reasons other than anaemia, depression and cardiopathy. Erythropoietin, in addition to its fundamental role in promoting erythrocyte production, would exert direct nervous effects by reducing the intensity of fatigue, but the results are still controversial (5). In any case, at present it is known that there are two fundamental inter-neuronal brain circuits, consisting of opioid (6) and cannabinoid systems (3), The opioid system is mainly related to the control of pain and stress, whereas the cannabinoid one is involved in the perception of pleasure and in the amplification of sensitivity and emotions. In addition, more recently it has been demonstrated the existence of a third fundamental inter-neuronal brain system, represented by ACE-ACE2 system (7). ACE is the enzyme responsible for producing angiotensin II (Ang II), while ACE2 is involved in the production of angiotensin 1-7 (Ang 1-7), the so-called angioliberine (8). At brain level, ACE2 receptors are expressed by neurons, glial cells, and endothelial cells. Neurons expressing ACE-ACE2 receptors are widely present into the brain, particularly localized into the motor cortex, amygdala, hypothalamus, raphe, and nuclei involved in the control of cardiovascular function (9). Then, ACE-ACE2 system would be involved in motor, cognitive and emotional functions. Moreover, a local renin-angiotensin system has been also documented in the pineal gland (10). Finally, it has been shown that ACE2/Ang 1-7/Mas receptor axis would play a fundamental role in several neurological and psychological conditions, including mood disorders, cerebrovascular ischemic and haemorrhagic diseases, and neurodegenerative pathologies (11). In more detail, the biological effects of Ang 1-7 are opposite with respect to those played by Ang II. In fact, Ang II has appeared to promote neuroinflammation and endothelial alterations responsible for ischemic and haemorrhagic brain disorders. From this point of view, in addition to IL-17 and endothelin-1 (ET-1), Ang II may be considered one of the most toxic endogenous molecules because of its hypertensive, inflammatory, pro-tumoral, pro-thrombotic and pro-fibrotic activities (11). Similar effects are played by both IL-17 (12) and ET-1 (13), which have also appeared to stimulate Ang II secretion, by constituting a positive feedback circuit (14,15). On the contrary, Ang 1-7 may act as a neuroprotective molecule by reducing neuroinflammation, neuronal apoptosis, oxidative stress, and infarct size (16). Therefore, asthenia could also be influenced by Ang II-Ang 1-7 balance. As well as Ang 1-7, cannabinoids (3) and MLT (4) may also play a neuroprotective action and an inhibitory effect on the neuroinflammatory processes. Moreover, the ACE-ACE2 system has appeared to be under a pineal regulatory control, since MLT has appeared to inhibit ACE expression and to promote that of ACE2 and the following Ang 1-7 production (17). Brain ACE system would be mainly connected to the opioid system, whereas ACE2 activity would be mainly connected to cannabinoid-pineal axis. Then, because of the involvement of cannabinoids and pineal in pleasure perception and mood, asthenia could be due at least in part on a functional deficiency of cannabinoid-pineal-Ang 1-7 brain axis. On these bases, a study was planned with MLT plus Ang 1-7 in the treatment of asthenia due to different causes.

PATIENTS AND METHODS

The study included 72 consecutive patients (M/F: 38/34; median age: 55 years, range 15-83) suffering from asthenia depending on specific diseases. Eligibility criteria were, as follows: important or moderate asthenia for more than one month, absence of important anaemia, no clinical evidence of depression, no concomitant psychopharmacological therapy, and no relevant dyspnoea. After the approval by the Ethical Committee, the clinical experimental protocol was explained to each patient, and written consent was obtained. The reasons responsible for asthenia were, as follows: advanced cancer: 23; Covid19 symptomatic infection: 17: post-Covid 19 syndrome: 15; cardiopathy: 7; neurodegenerative diseases: 4; multiple sclerosis: 3; diabetes mellitus: 3. Moreover, tumour histotypes were, as follows: glioblastoma: 5; colorectal cancer: 4; lung cancer: 3; pancreatic cancer: 3; breast cancer: 3; sarcoma: 3; biliary tract cancer: 2. MLT was given orally at a dose of 100 mg/day in the evening, according to its physiological light/dark circadian rhythm (4). Ang 1-7 was also given orally in gastro-protected capsules at a dose of 0.5 mg twice/day (8 AM and 8 PM). The treatment was continued for one month without interruption. Ang 1-7 was given at low dosage because of the possible amplification of its biological activity through a concomitant administration of the pineal hormone MLT (17). The supportive care also included other natural agents, mainly 5-methoxytryptamine, cannabidiol, Magnolia and Lotus extracts. Asthenia was assessed through self-analysis by assigning 1 point to low asthenia, 2 points to

mild asthenia, 3 points to important asthenia and 4 points to severe asthenia. Moreover, the degree of asthenia of patients was evaluated in relation to the immune status, as assessed by detecting lymphocyte-to-monocyte ratio (LMR), since whose decline has appeared to reflect the degree of the inflammatory immunosuppressive status (18). Normal values of LMR observe in our laboratory (95% confidence limits) was greater than 2.1. Data were reported as mean +/- SE, and statistically evaluated by the chi-square test and the Student's t test.

RESULTS

A severe asthenia was present in 18/72 (25%). An important asthenia occurred in 21/72 (29%), while asthenia was moderate in 23/72 (32%) patients, and low in the remaining 10 (14%) patients. A progressive relief of asthenia was achieved in 51/72 (71%) patients, and it was obtained within the first two weeks of therapy. Then, the mean values of asthenia subjective score significantly decreased on therapy (2.9 +/- 0.3 vs 1.4 +/- 0.4, P<0.05). Moreover, as shown in Table 1, the relief of asthenia was not related to the type of pathology, since no significant difference was seen in the percentage of efficacy in relation to the various pathologies. No therapy-related toxicity was seen, and particularly no important decline in blood pressure values occurred on Ang 1-7 treatment. On the contrary, most patients referred an improvement in well-being and sleep quality, as well as a relief of anxiety. Finally, an evident increase in diuresis volume was referred by 53/72 (74%) patients. As far as changes in the immune status are concerned, the control of asthenia was associated with a concomitant increase in LMR, and LMR mean values observed after one month of therapy in patients, who achieved a relief of asthenia, were significantly higher than in patients, who obtained no benefit from the treatment (3.4 +/- 0.3 vs 2.3 +/- 0.2, P< 0.05), while no difference was seen prior to therapy (2.4 +/- 0.4 vs 2.1 +/- 0.3).

Table 1: Percentage of Efficacy in the Treatment of Asthenia by Melatonin Plus Angiotensin 1-7 In Relation to the Type of Pathology.

PATHOLOGY	n	PERCENTAGE OF EFFICACY
OVERALL PATIENTS	72	51/72 (71%)
ADVANCED CANCER	23	15/23 (65%)
COVID19 INFECTION	17	13/17 (76%)
POST-COVID19 SYNDROME	19	15/19 (68%)
CARDIOPATHY	7	3/7 (43%)
NEURODEGENERATIVE DISEASES	4	2/4 (50%)
MULTIPLE SCLEROSIS	3	1/3 (33%)
DIABETES MELLITUS	3	2/3 (66%)

DISCUSSION

The results of this study show that the neuroendocrine regimen with high-dose MLT plus low-dose Ang 1-7 may be effective in the treatment of asthenia due to systemic diseases. MLT alone was also appeared to induce some benefits in advanced cancer patients with asthenia (19), with, however, lower results than those reported in the present study with MLT plus Ang 1-7.. As far as the mechanisms of action are concerned, since the inflammatory status is characterized by an enhanced secretion of inflammatory cytokines, namely IL-17A and IL-6, it is probable that both MLT and Ang1-7 may be effective in the treatment of asthenia by acting on both brain neurotransmissions and on cytokine network, because of the connections occurring between nervous system and cytokine network. Moreover, it has been shown that the inflammatory cytokines may influence the neurotransmitter pathways and induce changes in mood and status of consciousness (20). Therefore, the

symptom of fatigue may depend not only on brain neurochemical conditions, but also on the endogenous secretion of cytokines. Since human systemic diseases are characterized by an enhanced secretion of inflammatory cytokines, which may influence the nervous functions, MLT and Ang 1-7 may be effective in the treatment of asthenia by inhibiting the secretion of inflammatory cytokines. This statement is justified by the evidence that the relief of asthenia has appeared to be associated with an increase in LMR, since the occurrence of an important decline in LMR values has been shown to reflect the intensity of the inflammatory status (18). In fact, both MLT (21) and Ang 1-7 (8) have been proven to inhibit the secretion of inflammatory cytokines, namely that of IL-17 itself.

CONCLUSION

These results would justify further randomized studies with ML alone versus MLT plus Ang 1-7 to confirm whether the association of Ang 1-7 may clearly enhance the efficacy of MLT in the treatment of asthenia. Moreover, must be remembered that cytokine secretion is also under a neuroendocrine control, and on the other hand, nervous system function is influenced by cytokines, Therefore, further studies by monitoring changes in the secretion of inflammatory cytokines will be required to establish whether the efficacy of MLT plus Ang 1-7 in the treatment of chronic inflammatory disease-related asthenia may be due at least in part to an inhibition of cytokine-induced inflammatory status.

REFERENCES

1. Donna B G. Clinical dimensions of fatigue. Prim Care Companion J Clin Psychiatry 4:90-93, 2002.
2. Young P, Finn BC, Bruetman J, Pellegrini D, Kremer A. The chronic asthenia syndrome: a clinical approach. Medicina (B Aires) 70: 284-290, 2010.
3. Grotenhermen F. Pharmacology of cannabinoids. Neuroendocrinol Lett25: 14-23, 2004.
4. Brzezinski A. Melatonin in humans. N Engl J Med 336: 186-195, 1997.
5. O'Shaughnessy JA. Effects of epoetin on cognitive functions, mood, asthenia, and quality of life in women with breast cancer undergoing adjuvant chemotherapy. Clin Breast Cancer (Suppl 3): S116-S120, 2002.
6. Manfredi B, Sacerdote P, Bianchi M. Evidence for an opioid inhibitory tone on T cell proliferation. J Neuroimmunol 44: 43-46, 1993.
7. Jackson L, Eldahshan W, Fagan SC, Ergul A. Within the brain: the renin angiotensin system. Int J Mol Sci 19: 876, 2018.
8. Lissoni P, Porro G, Rovelli F, Lissoni A, Orfanò S, Galbanini J, Messina GH, Merlini D, Porta E, Di Fede G. A review on the potential therapeutic properties of angiotensin 1-7 in most systemic human diseases. Clin Res Hematol 3: 1-6, 2020.
9. Xia H, Lazartigues E. Angiotensin-converting enzyme 2in the brain: properties and future direction. J Neurochem 107: 1482-1494, 2008.
10. Baltatu O, Lippoldt A, Hansson A, Ganten D, Bader M. Local renin-angiotensin system in the pineal gland. Brain Res Mol Brain Res 54: 237-242, 1998.
11. Ribeiro VT, Crus de Souza L, Simoes-e-Silva AC. Renin-angiotensin system and Alzheimer's disease pathophysiology: from the potential interactions to therapeutic perspectives. Protein Pept Lett 27: 1-26, 2020.
12. Korn T, Bettelli E, Oukka M, Kuchroo VK. IL.-17 and Th1tcells. Annu Rev Immunol 27: 485-517, 2009.
13. Grant K, Loizidou M, Taylor I. Endothelin-1: a multifunctional molecule in cancer. Br J Cancer 88: 163-166, 2003.
14. Madhur MS, Lob HE, McCann LA, Iwakura Y, Blinder Y, Guzik FJ, Harrison DG. Interleukin-17 promotes angiotensin II-induced hypertension and vascular dysfunction. Hypertension 55. 500-507, 2010.
15. Zhang H, Li Y, Zeng Y, Wu R, Ou J. Endothelin-1 downregulates angiotensin-converting enzyme-2 expression in human bronchial epithelia cells. Pharmacology 91: 2967-302, 2013.
16. Almeida-Santos AF, Kangussu LM, Campagnole-Santos MJ. The rein-angiotensin system and the neurodegenerative diseases: a brief review. Protein Pept Lett 24: 841-853, 2017.
17. Campos LA, Cipolla-Neto J, Amaral FG, Michelini LC, Bader M, Baltatu OC. The angiotensin-melatonin axis. doi: 10.1155/2013/521783, 2013.
18. Gu L, Li H, Chen L, Ma X, Li X, Gao Y, Zhang Y, Xie Y, Zhang X. Prognostic role of lymphocyte-to-monocyte ratio in patients with cancer: evidence from a systematic review and meta-analysis. Oncotarget 3: 7876-7881, 2016.
19. Lissoni P. Is there a role for melatonin in supportive care? Supp Care Cancer 10: 110-116, 2000.
20. Riley V. Psychoneuroendocrine influence on immunocompetence and neoplasia. Science 212: 1100-1109, 1981.
21. Kuklina EM, Glebezdina NS, Nekrasova IV. Role of melatonin in the regulation off differentiation of T cells producinginterleukin-18(Th17). Bull Exp Biol Med 160: 656-658, 2016.

How to cite this article: Lissoni P, Porro G, Lissoni A, Porro D, Rovelli F, Aliboni G, Mantoani M, Di Fede G, Valentini A, Colciago M Silva A, Cardinali D. The Enygma of Asthenia: A Study of Angiotensin 1-7 and Melatonin in the Treatment of Asthenia Induced by Different Pathological Conditions. Clin Res Hematol 2021;4(1):4-7. DOI: 10.33309/2639-8354.040102