RESEARCH WORK

Neuroimmune Therapy of Autoimmune Diseases with the Pineal Hormone Melatonin Plus Cannabidiol and its Effects on Auto-Antibody Secretion

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ABSTRACT

Today, it is known that autoimmune disease-related abnormal production of auto antibodies is mainly induced by an increased IL-17 secretion in association with a concomitant diminished T reg cell function. Then, the inhibition of IL-17 secretion could allow a control of the autoimmune processes. IL-17 production has also appeared to be under a neuroendocrine control, and it may be inhibited by the pineal hormone melatonin (MLT) and cannabinoid agents, such as cannabidiol (CBD). On these bases, a study was planned to evaluate the influence of a neuroimmune regimen with MLT plus CBD on some autoantibody production in patients with autoimmune diseases. The study included 14 patients suffering from autoimmune diseases with abnormally high levels of ANA, Rheumatoid Factor or anti-thyroglobulin (TG) antibody levels. MLT was given orally at 20 mg/day in the evening, and CBD was also administered orally at 10 mg twice/day. The treatment was continued for 3 consecutive months. The mean values of all autoantibodies significantly decreased on treatment, and no exacerbation of disease was noted. Therefore, these preliminary results seem to suggest that autoimmune disease-related enhanced autoantibody production may be controlled by a neuro-immunotherapeutic approach with MLT plus CBD. Further studies will be necessary to evaluate the impact of the diminished autoantibody secretion on the clinical course of the autoimmune pathologies.

Key words: ANA, Autoimmune diseases, Cannabinoids, Melatonin, Neuroimmunomodulation, Rheumatoid Factor.

INTRODUCTION

Autoimmune diseases are defined by the evidence of an abnormally high auto-antibody production against one or more self-antigens of the different organs. However, auto-antibody increase secretion would not represent the primary pathogenetic even, but it simply represents the consequence of an altered function of the cytokine network in a pro-inflammatory way. In fact, the autoimmune diseases have appeared to be characterized by a non-specific increase in blood levels of several macrophage-related inflammatory cytokines, mainly IL-6, TNF-alpha and IL-1beta (1), whose exaggerated secretion correlates to the acute phase of disease. Moreover, more recently it has been shown that IL-17 (2) released from Th17 lymphocytes plays a fundamental role in the pathogenesis of the autoimmune processes by either inhibiting regulatory T (T reg) lymphocytes (3), which in contrast counteract the inflammatory response (4), or promoting the activation of the macrophage system (5). Then, the evidence of abnormally high levels of IL-17, mainly of the IL-17A isoform, is associated with a worse prognosis. On the contrary, the occurrence of increased levels of TGF-beta (6) and IL-10 (7) is associated with a disease control. Therefore, the inhibition of IL-17 secretion or the stimulation of TGF-beta

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and IL-10 production would allow a control of disease. The secretion of each single cytokine is regulated by the cytokine network. In more detail, IL-17 secretion is inhibited by both IL-2 (8) and IL-12 (9) and TGF-beta, which in contrast may stimulate IL-17 production in the association with IL-6 or IL-23 and IL-22 (10, 11). Finally, TGF-beta secretion is inhibited by IL-21, which is mainly released from Th1 lymphocytes (12). In addition, the recent advances in the area of the psycho-neuro-endocrine-immunology (PNEI) have shown that immune system and cytokine network are physiologically under a neuroendocrine system (13), mainly played by the pineal gland through its most known indole hormone melatonin (MLT) (14) and brain cannabinoid (15) and opioid systems (16). Both endogenous cannabinoids arachidonyl-ethanol-amide and 2-arachidonyl-glycerol and exogenous cannabinoid tetra-hydroxy-cannabinol (THC) (15,17), as well as the pineal hormone MLT (18), have appeared to inhibit IL-17 secretion, whereas the opioid agonists, mainly the mu-agonists ones, would exert a prevalent stimulatory action (19). The non-psychoactive of Cannabis cannabidiol (CBD) has also been proven to reduce IL-17 secretion (17) by inhibiting the activity of fatty acid amide hydrolase (FAAH), the enzyme involved in cannabinoid degradation (20), with a following increase in cannabinoid endogenous content. Finally, within the group of the therapeutic plants, honokiol, the main active component of Magnolia, has also been proven to counteract IL-17 secretion (21). As far as the group of auto-antibodies (22), anti-thyroglobulin (TG) antibodies are specific of Hashimoto's thyroiditis, while antinuclear antibodies (ANA) and Rheumatoid Factor, an anti-IgG globulin, may characterized several systemic connective tissue diseases, even though the evidence of high levels of ANA and FR are commonly more typical of systemic lupus erythematous (SLE) and rheumatoid arthritis (RA), respectively. At present, the possible therapeutic role of MLT in autoimmunity is still controversial, because of its potential immunostimulatory activity on most immune functions (14). The immunostimulatory action of MLT, however, would mainly involve the cellular immunity, including the anticancer immunity (14), rather than the humoral one. Moreover, the inhibitory effect of MLT on IL-17 could opposite the progression of the autoimmune disease (18), either alone or in combination with cannabinoid agents, which may also suppress IL-17 production and activity (15, 17). On these bases, a study was planned to evaluate the influence of a combination between MLT and cannabinoid agents on the production of some of the most commonly auto-antibodies, including ANA, Rheumatoid Factor and anti-TG antibodies.

MATERIALS AND METHODS

The study included 14 consecutive patients with the diagnosis of autoimmune pathology, consisting of Hashimoto's thyroiditis with high levels of anti-thyroglobulin (TG) antibodies (n=4) and various systemic connective tissue diseases (CTD) with high titres of ANA (n=6) or Rheumatoid Factor (n=4). The systemic CTD were, as follows: SLE: 2; RA: 4; mixed connective disease: 3; systemic sclerosis: 1. Patients under chronic therapy with corticosteroids or immunosuppressive agents were not included in the study. After ethical approvement, the experimental protocol was explained to each patient, and written consent was obtained. MLT was given orally at 20 mg one daily during the dark period of the day in relation to its circadian light/dark rhythm, generally 30 minutes prior to sleeping. We decided to use MLT only at mild pharmacological doses, since the anti-inflammatory action of MLT would depend on its dose, and at very pharmacological doses it could exert a pro-inflammatory action (23). On the contrary, the antitumor action of MLT has appeared to be a dose-dependent phenomenon (24). CBD was given orally at a dose of 10 mg twice/day (8.00 AM and 8.00 PM). The treatment was continued without interruption for 3 consecutive months, by detecting autoantibody levels before and after one and three months of therapy. Normal values obtained in our laboratory (95% confidence limits) were below 1: 40 for ANA, below 14 IU/ml for Rheumatoid Factor, and below 30 IU/ml for anti-TG. Anti-TG autoantibodies and Rheumatoid Factor values were measured by an enzyme immunoassay, while ANA titre was determined by an indirect fluorescent assay, by using in both cases commercially available kits. Data were reported as mean +/- SE, and statistically analysed by the Student's t test.

RESULTS

A decline in auto-antibody levels greater than 30% was achieved after 3 months of therapy in 11/14 (78%) patients (anti-TG: 3/4(75%); Rheumatoid Factor: 3/4(75%); ANA: 5/6(83%). Moreover, as reported in Table 1, mean values of auto-antibody levels observed after three months of therapy were significantly lower than the values observed prior to therapy (ANA: $P<0.05$; anti-TG: $P< 0.025$; Rheumatoid Factor: $P<0.05$). The treatment was well tolerable in all patients, and no clinical exacerbation of the symptomatology occurred on study. On the contrary, most patients experienced a relief of anxiety and a better perception of pleasure.

Table 1. Changes in autoantibody levels (mean +/- SE) on neuroimmune therapy with melatonin plus cannabidiol.

AUTOANTIBODIES	BEFORE	AFTER 1 MONTH	AFTER 3 MONTHS
ANTI-TG (IU/ml)	368 +/- 44	244 +/- 51	128 +/- 35**
ANA	1: 240 +/- 40	1:160 +/- 40	1: 80 +/- 20*
RHEUMATOID FACTOR (IU/ml)	88 +/- 11	66 +/- 1042 +/- 7*	

*P<0.05; ** P< 0.025

DISCUSSION

This preliminary phase 2 studies shows that the neuroimmune combination carried out to inhibit IL-17 secretion with the pineal indole MLT plus the cannabinoid agent CBD (17, 18), is a well tolerable treatment in patients with different kinds of autoimmune disease and an effective therapy in reducing autoantibody production. Obviously, further studies by monitoring changes in IL-17 blood concentrations will be needed to establish whether the decline in autoantibody levels induced by MLT plus CBD may be the consequence of their inhibitory action on IL-17 production. In addition, as far as ANA values are concerned, further researches will have to investigate which ANA subtype may be particularly influenced by the treatment. Moreover, further randomized studies will be necessary to evaluate whether the combination of MLT plus CBD may be more effective with respect to the single agents. Finally, longitudinal studies will be required to establish whether MLT and CBD-induced decline in autoantibody production may positively influence the clinical course of the autoimmune diseases.

CONCLUSION

Since the autoimmune diseases are due to a diminished T reg cell function and TGF-beta production in association with an abnormally enhanced IL-17 secretion, TGF-beta-to-IL-17 ratio, as well as T reg-to-Th17 ratio, could constitute the most simple and adequate biomarker to monitor the clinical evolution of the autoimmune disorders, and the evidence of a progressive rise in TGF/IL-17 ratio would be a sign of disease control.

REFERENCES

1. Maczynska I, Millo B, Ratajczak-Stefanska V, Maleszka R, Szych Z, Kurpisz M, Giedrys-Kalemba S. Proinflammatory cytokine (IL-1beta, IL-6, IL-12, IL-18 and TNF-alpha) levels in sera of patients with subacute cutaneous lupus erythematosus (SCLE). ImmunolLett 102: 79-82, 2006.
2. TabarkiewiczJ, Pogoda K, Karczmarczyk A, Pozarowski P, Giannopoulos K. The role of IL-17 and Th17 lymphocytes in autoimmune diseases. Arch Immunol Ther Exp (Warsz) 63: 435-439, 2015.
3. Korn T, Bettellli E, oukka M, Kuchroo VK. IL-17 and Th17 cells. Annu Rev Immunol 27: 485-517, 2009.
4. Afzali B, Lombardi G, Lechler RI, Lord GM. The role of T helper 17 (Th17) and regulatory T cells (T reg) in human organ transplantation and autoimmune disease. ClinExpImmunol 148: 32-46, 2007.
5. Kryczek I, Wei S, Vatan L, Escara-Wilke J, Szeliga W, Keller ET, Zou W. Cutting edge: opposite effects of IL-1 and IL-2 on the regulation of IL-17+ T cell pool IL-1 subverts IL-2-mediated suppression. J Immunol 179: 1423-1426, 2007.
6. Paramalingam SS, Thumboo J, Vasoo S, Thio ST, Tse C, Fong KY. In vivo pro- and anti-inflammatory cytokines in normal and patients with rheumatoid arthritis. Ann Acad Med Singapore 36: 96-99, 2007.
7. Heo YJ, Joo YB, Oh HJ, Park MK, Heo YM, Cho ML, Kwok SK, Ju JH, Park KS, Cho SG, Park SH, Kim HY, Min JK. IL-10 suppresses Th17 cells and promotes regulatory T cells in the CD4+ T cell population of rheumatoid arthritis patients. Immunol Lett 127: 150-156, 2010.
8. Laurence A, Tato CM, Davidson TS, Kanno Y, Chen Z, Yao Z, Blank RB, Meylan F, Siegel R, Hennighausen L, Sjevack EM, O'shea JJ: Interleukin-2 signaling via STAT5 constrains T helper 17 cell generation. Immunity 26: 371-381, 2007.
9. Murphy CA, Langrish CL, Chen Y, Blumenschein W, McClanahan T, Kastelein RA, Sedgwick JD, Cua DJ. Divergent pro- and anti-inflammatory roles for IL-23 and IL-12 in joint autoimmune inflammation. J Exp Med 198: 1951-1957, 2003.
10. Barbi J, Pardoll D, Pan F. Metabolic control of the T reg/Th17 axis. Immunol Rev 252: 52-77, 2013.
11. Hoeve MA, Savage ND, de Boer T, Langenberg DM, de Waal Malefyt R, Ottenhoff TH, Verreck FA. Divergent effects of IL-12 and IL-23 on the production of IL-17 by human T cells. Eur J Immunol 36: 661-670, 2006.
12. Battaglia A, Buzzonetti A, Baranello C, Fanelli M, Fossati M, Catzola V, Scambia G, Fattorossi A. Intereleukin-21 (IL-21) synergizes with IL-2 to enhance T cell receptor-induced human T cell proliferation and counteracts IL-2/transforming growth factor-beta-induced regulatory T cell development. Immunology 139: 109-120, 2013.
13. Rubinow DR. Brain, behaviour and immunity: an interactive system. J Natl Cancer Inst Monogr 10: 79-82, 1990.
14. Maestroni GJM. The immunoneuroendocrine role of melatonin. J Pineal Res 14: 1-10, 1993.
15. Grotenhermen F. Pharmacology of cannabinoids. Neuroendocrinol Lett 25: 14-23, 2004.
16. Manfredi B, Sacerdote P, Bianchi M. Evidence for an opioid tone on T cell proliferation. J Neuroimmunol 44: 43-46, 1993.
17. Nagarkatti P, Pandey R, Rieder SA, Hedge VL, Nagarkatti M. Cannabinoids as novel anti-inflammatory drugs. Future MedChem 1: 13334-1349, 2009.
18. Kuklina EM, Glebezdina NS, Nekrasova IV. Role of melatonin in the regulation of differentiation of T cells producing interleukin-17 (Th17). Bull ExpBiolMed 160: 656-658, 2016.
19. Liang X, Liu R, Chen C, Ji F, Li T. Opioid system modulates the immune function: a review. TranslPeriop Pain Med 1: 5-13, 2016.
20. Deutsch DG, Ueda N, Yamamoto S. The fatty acid amide hydrolase (FAAH). Prostaglandins Leukot Essent Fatty Acids 66: 201-210, 2002.
21. Fried LE, Arbiser JL. Honokiol, a multifunctional antiangiogenic

and antitumor agent.Antioxid Redox Signal 11: 1139-1148, 2009.

22. Moore TL. Laboratory studies in autoimmune diseases. Mo Med 113: 118-122, 2016.
23. Medrano-Campillo P, Sarmiento-Soto H, Alvarez-Sanchez N, Alvarez-Rios AI, Guerrero JM, Rodriguez-Prieto I, Castillo-Palma MJ, Lardone PJ, Carrillo-Vico A. Evaluation of the immunomodulatoryeffect of melatonin on the T cellresponse in periheparlblood from systemic lupus erythematosuspatients. J Pineal Res 58: 219-226, 2015.
24. Lissoni P, Messina G, Rovelli F Brivio F, Di Fede G. Dose-dependency of antitumor effects of the pineal hormonemelatonin in untreatable metastatic solid tumor patients. Int J Immunol Immunobiol 1: 1-3, 2018.

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