

A Review on the Potential Therapeutic Properties of Angiotensin 1-7 in Most Systemic Human Diseases

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ABSTRACT

COVID-19 disease has dramatically demonstrated the fundamental role of angiotensin-converting enzyme 2 and its active product angiotensin 1-7 (Ang 1-7) in the inhibitory control of cytokine-induced inflammatory response, whose importance was not taken into consideration in the clinical practices. On the contrary, several experimental and clinical studies have shown that Ang 1-7 in addition to its hypotensive and cardioprotective actions may also play anti-inflammatory, antitumor, antithrombotic, and antifibrotic effects, then a potential regenerative activity. Most systemic human diseases, including advanced cancer, autoimmunity, cardiovascular disease, neurodegenerative pathologies, metabolic syndrome, and aging itself would be characterized by a reduced Ang 1-7 production and activity. Unfortunately, despite its potential universal therapeutic properties and its lack of toxicity, at present, few clinical studies have been performed to evaluate the therapeutic efficacy of Ang 1-7 in the different human pathologies in an attempt to prolong the duration of life.

Key words: Aging, angiotensin 1-7, angiotensin-converting enzyme 2, autoimmunity, cancer, cannabinoids, cardiovascular diseases, metabolic syndrome

INTRODUCTION

It is known that the immune system reflects the evolution of the different living species. Moreover, it has been shown that the enhanced inflammatory status may be considered as the common mechanism responsible for the human systemic diseases, including cancer,^[1] autoimmunity,^[2] and cardiovascular disorders.^[3,4] In fact, cancer has been proven to be characterized by an abnormally enhanced production of both macrophage- and Th17 cell-related inflammatory cytokines,^[1,5] autoimmune processes would be mainly promoted by interleukin (IL-17),^[2] and both cardiac^[6] and cerebral ischemia^[7] have appeared to have a worse prognosis in the presence of a decline in lymphocyte count associated with an increase in monocyte number as a sign of the inflammatory status. Finally, today, it is known that the inflammatory status is depending on the functional status of the cytokine network,^[8] and that at this moment of the evolution of the immune system,

within the great number of cytokines, most of them are provided by an inflammatory action,^[8] including IL-1 beta, IL-6, tumor necrosis factor (TNF)-alpha, IL-8, and IL-17, and only few cytokines are characterized by a clear anti-inflammatory action, namely, IL-10^[9] and transforming growth factor (TGF)-beta,^[10] while IL-2^[11] and IL-12^[12] may exert both inflammatory and anti-inflammatory effects, because of their inhibitory action on the secretion and activity of IL-17, which would constitute the main inflammatory cytokine responsible for the human systemic disturbances, because of its pro-tumoral role,^[13] its involvement in the pathogenesis of the autoimmune diseases,^[2] and its toxic effects on cardiac, pulmonary, and endothelial functions,^[14] with as possible consequences respiratory distress,^[15] thrombosis, and cardiac ischemia.^[14] Moreover, IL-17 secretion is stimulated by endothelin-1 (ET-1),^[16] which plays also pro-tumoral, inflammatory action, and cardiovascular toxic effects.^[17] Unfortunately, the main anti-inflammatory cytokines, including TGF-beta and IL-10,

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are concomitantly provided by immunosuppressive activity on the anticancer immunity.^[9,10] Moreover, TGF-beta has appeared to stimulate IL-17 production in the presence of IL-6.^[10] The prevalence of the inflammatory cytokines would be physiologically counteracted and balanced by a fundamental anti-inflammatory neuroendocrine system, consisting of the pineal-cannabinoid functional axis,^[18] since both (melatonin [MLT]), the most investigated pineal indole hormone^[19] and cannabinoid agents^[20] have been proven to play an essential anti-inflammatory immunostimulatory role by modulating the cytokine network in an anti-inflammatory way,^[18] in particular by inhibiting IL-17 secretion,^[19,20] as well as that of IL-6 and TNF-alpha. MLT has also appeared to stimulate IL-2 secretion from Th1 lymphocytes.^[21] Then, MLT, either alone or in connection with the endocannabinoid system, and IL-17 would constitute two fundamental endogenous molecules in the regulation of the inflammatory status by exerting opposite effects, respectively, consisting of inhibition and activation of the inflammatory response.^[21] Moreover, pineal-cannabinoid axis and IL-17 would be connected by reciprocal inhibitory effects, since both MLT^[19] and cannabinoids^[20] inhibit IL-17 secretion, and IL-17, in turn, may allow an endocannabinoid deficiency by promoting the adipocyte release of leptin,^[22] which activates the fatty acid amide hydrolase (FAAH), the enzyme involved in cannabinoid degradation,^[20] with a consequent decline in cannabinoid endogenous content. MLT may inhibit IL-17 secretion either directly^[19] or by promoting IL-2 secretion,^[21] which is also able to inhibit IL-17 production.^[23] The end result of MLT-IL-17 interactions could consist of their influence on angiotensin-converting enzyme 2 (ACE2) receptor expression, the enzyme involved in the generation of angiotensin 1-7 (Ang 1-7), whose anti-inflammatory, antiangiogenic, antiproliferative, antithrombotic, and antifibrotic activities have been recently well demonstrated.^[24-27] ACE2 expression is stimulated by MLT^[28] and inhibited by IL-17.^[29] Then, in addition to their direct biological effects, MLT and IL-17 would also exert their opposite effects by modulating ACE-ACE2 expression, then, respectively, the production of angiotensin II (Ang II) and Ang 1-7. Moreover, it appears that the anti-inflammatory action of MLT,^[30] cannabinoids,^[31] and Ang 1-7^[24-27] is constantly associated with an antiproliferative, antiangiogenic, and antitumoral activity, by furtherly confirming the association between inflammation and cancer progression.^[1] MLT and Ang 1-7 would exert their potential regenerative action in a different and complementary ways, the pineal hormone MLT in relation to the environmental universal conditions, mainly the light/dark circadian rhythm, by modulating DNA expression,^[32] and Ang 1-7 in relation to the biological conditions and their progressive age-related diminished functionless.^[24-27] In fact, age-related decline in ACE2 expression, with a following diminished production of Ang 1-7 itself, has appeared to be involved in the onset of atherosclerosis, cardiac and brain ischemic disorders, hypertension, pulmonary arterial hypertension, metabolic syndrome with insulin resistance, and probably

cancer itself.^[24-27] In contrast, IL-17 production enhances with age,^[33] and age-related increased IL-17 secretion could be due at least in part to the decline in MLT nocturnal production with age^[32] because of the inhibitory action of MLT on IL-17 secretion^[19] and could be responsible for age-related decline in Ang 1-7 production^[34] because of the inhibitory action of IL-17 on ACE2 expression and the stimulatory one on that of ACE.^[29] Finally, ACE2-Ang 1-7 and cannabinoid systems would be connected by reciprocal stimulatory actions, since cannabinoids have appeared to promote ACE2 expression and Ang 1-7 production,^[35] which, in turn, stimulates cannabinoid receptor expression.^[36] Therefore, one of the fundamental parameters of the status of health could be represent by the ratio between IL-17 and Ang 1-7 blood levels, because of their opposite effect on the inflammatory status and fibrotic processes. In addition to Ang 1-7, oxytocin is also provided by cardioprotective effects, being involved in the heart regeneration.^[37] Unfortunately, few clinical studies only have been performed up to now the investigate Ang 1-7 secretion in the different human systemic pathologies. MLT-IL-17 interactions in the regulation of Ang 1-7 production and their influence on the most important human systemic diseases are illustrated in Figure 1.

BIOLOGY OF ANG 1-7

Ang 1-7 is one of the main products of renin-angiotensin system. In more detail, the angiotensinogen synthesized at hepatic level is transformed into angiotensin I (Ang I) through the action of the protease renin produced by the juxtaglomerular renal cells.^[24-27] Then, Ang I may be degraded into Ang II by ACE and into Ang 1-7 by ACE2, which is also able to transform Ang II into Ang 1-7. Ang II exerts its hypertensive, inflammatory, pro-fibrotic, and protumoral effects by acting on Ang II receptor type 1, whereas Ang 1-7 plays its opposite hypotensive, anti-inflammatory,

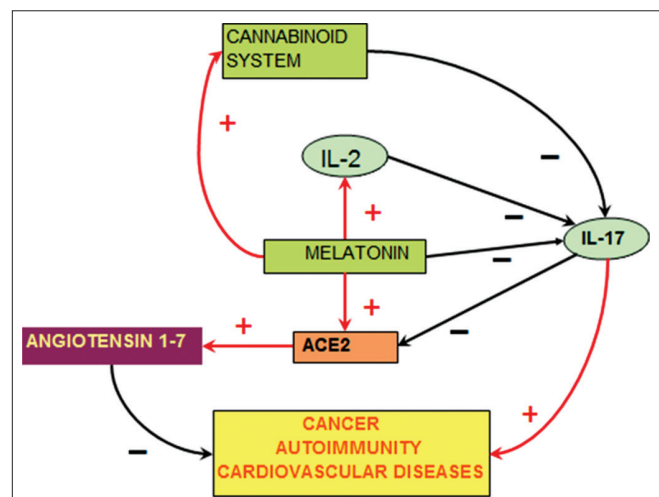


Figure 1: Melatonin and interleukin-17 opposite effects on angiotensin 1-7 secretion

antifibrotic, and antitumoral effects by acting on MAS receptor. ACE2 may also transform Ang II into Ang 1-7. Finally, Ang 1-7 may be produced not only by ACE2 but also through the action of other proteases, the so-called vasopeptidase, the most important of them would be the neprilysin,^[24-27] which is the enzyme responsible for the degradation of both Ang 1-7 and Ang II.

HEMATOLOGIC AND IMMUNE PROPERTIES OF ANG 1-7

Ang 1-7 has been proven to be involved in bone marrow growth and differentiation, mainly by stimulating lymphocyte and megakaryocyte proliferation, whereas it would inhibit monocyte generation.^[38] Then, the main immune and hematologic effects of Ang 1-7, consisting of increase in both lymphocyte and platelet count, are very similar to those of MLT, which has also appeared to stimulate lymphocyte^[21] and platelet generation,^[39] by furtherly remarking the connections between MLT and Ang 1-7 effects. Preliminary clinical studies have confirmed the ability of Ang 1-7 to protect against chemotherapy-induced lymphopenia and thrombocytopenia. Therefore, by considering that there is no clinical guideline for the treatment of lymphopenia and thrombocytopenia, the stimulatory effect of MLT and Ang 1-7 on lymphocyte and platelet production could deserve a fundamental clinical relevance.

THE ANTICANCER ROLE OF ANG 1-7 AND ITS MECHANISMS

All standard drugs employed in the treatment of cancer exert their activity substantially through four fundamental biological mechanisms, consisting of direct antiproliferative cytotoxic action, antiangiogenic action, and immunostimulatory activity on the anticancer immunity. From this point of view, Ang 1-7, as well as the pineal hormone MLT,^[30] may play its anticancer activity by exerting all potential antitumor actions, including inhibition of cancer cell proliferation, antiangiogenic action by counteracting VEGF secretion, and immunostimulating effects by promoting lymphocyte differentiation and inhibiting the activity of the monocyte-macrophage system,^[40-42] which on contrast suppresses the anticancer immunity.^[1] According to experimental investigations and preliminary clinical studies,^[40-42] Ang 1-7 could be potentially active against all tumor histotypes, including common and triple negative breast cancer, glioblastoma, sarcomas, lung cancer, hepatocarcinoma, and prostate cancer. Moreover, Ang 1-7 could reduce the possible radiotherapy- and chemotherapy-induced suppression of the anticancer immunity by protecting against lymphopenia.^[36] Finally, Ang 1-7 could be active in the palliative therapy of cancer pain.^[43]

THE PROTECTIVE ACTION OF ANG 1-7 ON LUNG AND CARDIOVASCULAR SYSTEM

In contrast to Ang II, which induces hypertension, cardiac hypertrophy, endothelial damage and consequent thrombotic effects, and atherosclerosis, Ang 1-7 determines hypotensive, anti-ischemic cardioprotective, antithrombotic, and antifibrotic effects, by contributing to the regeneration of the cardiovascular system.^[24-27] Ang 1-7 has also appeared to be active in the treatment of pulmonary arterial hypertension.^[44] Finally, ACE-ACE2 system has also appeared to interact with ANP-ET-1 axis with opposite effects, since ET-1 has appeared to inhibit ACE2 expression and to stimulate the expression of ACE.^[45] In contrast, Ang 1-7 stimulates ANP secretion either directly or through its transformation into angiotensin 1-5,^[46] and Ang 1-7-induced ANP release would explain its diuretic effect, because of the fundamental natriuretic role of ANP.^[47] The low frequency of cardiovascular disorders in premenopausal women could be due to the stimulatory action of estrogens on ACE2 expression.^[48] Moreover, ANP may exert opposite systemic effects with respect to ET-1, since ANP plays anti-inflammatory and antitumor effects,^[47] whereas ET-1 has been proven to have pro-inflammatory and pro-tumoral activities.^[17] Finally, Ang 1-7 and Ang II would exert opposite effects on the connexins of gap intercellular junctions, which may be altered by both AT-1 and Ang II and protected by Ang 1-7.^[49]

ANG 1-7 AND NEURODEGENERATIVE DISEASES

Irrespectively of the different types of neurodegenerative pathologies, including Alzheimer's disease, Parkinson's disease, multiple sclerosis, encephalitis, and amyotrophic lateral sclerosis, the neurodegenerative diseases are induced by an abnormal neuroinflammatory status.^[50] Moreover, the neuroinflammation has appeared to be induced by an enhanced production of inflammatory cytokine, including IL-6 and TNF-alpha, by the glial cells and mast cells into the brain. In addition, it has been shown the existence of an ACE-ACE2 system also at brain level, and a diminished ACE2 expression has been documented in neurodegenerative disease, such as multiple sclerosis. Therefore, because of its fundamental anti-inflammatory activity, the neuroinflammation could be due at least in part on an Ang 1-7 deficiency into the brain. In fact, Ang 1-7 has appeared to exert neurotrophic and neuroprotective effects and to be potentially active in the treatment of the peripheral neuropathy.^[51] Finally, Ang 1-7 has been proven to protect against brain ischemia and stroke.^[52]

ANG 1-7 AND AUTOIMMUNITY

According to the knowledgments available up to now, the main cytokine responsible for the pathogenesis of the

autoimmune diseases is IL-17^[2] because of its inhibitory action on regulatory T lymphocytes, whose fundamental anti-inflammatory immunosuppressive role is well known. Moreover, it has recently been shown that autoimmune disease may be associated with a diminished secretion of Ang 1-7.^[53] Then, because of the inhibitory action of IL-17 on ACE2-induced Ang 1-7 production,^[29] autoimmunity-related Ang 1-7 deficiency could be the simple consequence of IL-17 overproduction.

ANG 1-7 IN THE METABOLIC SYNDROME

The metabolic syndrome, substantially characterized by an enhanced insulin resistance in association with adiposity, lipid metabolism alterations, and hypertension, has recently been to reflect an enhanced inflammatory status due to an enhanced production by adipocytes of leptin, which stimulates the adipocyte production of inflammatory cytokines, including iL-6 and TNF-alpha.^[54] Moreover, leptin has appeared to stimulate ACE expression and inhibit that of ACE2, with a consequent diminished production of Ang 1-7. Finally, leptin may allow an endocannabinoid deficiency by stimulating FAAH activity, with a following diminished endocannabinoid content^[55] that determines an enhanced production of IL-17, which furtherly promotes an enhanced inflammatory cytokine production by adipocytes and the inhibition of ACE2 expression. Therefore, according to its anti-inflammatory effect, Ang 1-7 therapy could counteract leptin-induced inflammatory status caused by an enhanced adipocyte production of inflammatory cytokines.

ANG 1-7 IN COVID-19 INFECTION

The link of viral spike protein (SP) to ACE2 receptor on cell surface does not only induce the entry of the virus into the cells but also a block of ACE2 activity, with a consequent diminished production of Ang 1-7 and an acute Ang 1-7 deficiency.^[56] In addition, viral SP interaction with ACE2 would allow the activation of the enzyme FAAH,^[57] with a consequent enhanced cannabinoid degradation and an acute endocannabinoid deficiency, which furtherly amplify the inflammatory response of patients because of the inhibitory role of cannabinoids on IL-17 secretion. Finally, the increased IL-17 production furtherly enhances the inhibition of ACE2 expression and activity. Moreover, IL-17 promotes the macrophage release of other important inflammatory cytokines, including IL-6 and TNF-alpha. Finally, the abnormal IL-17 production induces endothelial damage, with a consequent increase in thromboembolic events, and enhances the alveolar-capillary permeability with consequently pulmonary edema and acute respiratory failure. Then, because the involvement of immune, endocrine, cardiovascular, and nervous system, COVID-19 disease would

represent the main acute psychoneuroendocrinoimmune (PNEI) pathology, as well as cancer represents the main chronic PNEI pathology.

ANG 1-7 AS A POTENTIAL ANTI-AGING NATURAL AGENT

Age has appeared to be associated with a progressive decline in both MLT secretion^[32] and Ang 1-7 production following the age-related diminished expression of ACE2.^[34] MLT has been confirmed to act as an anti-aging natural agent by counteracting free radical-induced DNA damage and connecting the biological system according to the universal light/dark rhythm.^[32] In any case, MLT would not represent the only anti-aging molecule of the pineal gland, since in experimental conditions, the transplantation of the pineal gland from young to old animals has been proven to prolong the life more than the administration of MLT alone.^[58] In a complementary way, Ang 1-7 would act as a natural anti-aging molecule by counteracting age-related fibrotic processes and promoting tissue repair and regeneration mainly at cardiac and brain levels. Osteoporosis could also obtain some benefit from Ang 1-7 therapy because of its documented inhibitory role on osteoclast proliferation and activity.^[59] By synthesizing, one of the main factors responsible for aging processes would be represented by IL-7, being toxic for several organs. Then, every molecule able to inhibit IL-17 secretion, including the pineal hormone MLT and cannabinoids such as cannabidiol (CBD), may act as anti-aging drug. Moreover, because of the inhibitory effect of IL-17 on Ang 1-7 production by counteracting ACE2 expression,^[29] which already declines with age, Ang 1-7 would be also essential to counteract age-related processes and promote tissue cell regeneration. Therefore, MLT, CBD, and Ang 1-7 would represent the main active molecules for the future anti-aging approaches.

THERAPEUTIC ACTIVITY OF ANG 1-7

According to the experimental investigation and the preliminary clinical studies, Ang 1-7 at a dose ranging from 0.5 to 5 mg/day^[39-44] is a well tolerable therapy, which could be potentially effective in the treatment of all human systemic diseases without any toxicity, at least to improve their prognosis, including advanced neoplasms, autoimmune pathologies, cardiac ischemia, hypertension, heart failure, respiratory distress, metabolic syndrome, and neurodegenerative diseases. The only precaution consists of the control of blood pressure, even though no important decline was described on therapy. One of the most subjective reported effects on Ang 1-7 therapy seems to consist of the relief of asthenia in both patients suffering from advanced tumors and cardiovascular diseases, which yet remains a subjective clinical symptom difficult to be

treated. Obviously, several years will be required to establish the real efficacy of Ang 1-7 in the treatment of human systemic diseases, irrespectively of their different physiopathology, but on the bases of the already existing experimental studies, the clinical investigation of the therapeutic properties of Ang 1-7, as well as that of MLT, could constitute one of the main areas of the future medicine.

CONCLUSIONS

According the recent advances in the area of PNEI, at present, it is possible to identify within the human biological body two fundamental functional axes, which consist of the interactions among pineal-cannabinoid system – ANP and Ang 1-7 axis, provide by anti-inflammatory, antitumoral, and cardioprotective effects, and among ET-1 and Ang II, provided by pro-inflammatory and pro-tumor activities. Then, these two functional axes could be respectively defined as the way of life and the way of death, according to the vision of the old Essenic medicine. The new medicine will required a new diagnostic clinical approach, with several laboratory parameters to be included into the routine clinical analysis, consisting of MLT rhythm to evaluate the pineal function, ET-1 and ANP to investigate the endocrine cardiac function, FAAH to analyze the functionless of the endocannabinoid system, and TGF-beta-to-IL-17 ratio by represent the main anti-inflammatory and pro-inflammatory cytokine, respectively. However, the end result of the interactions among these bioactive molecules could be simply represented by the only Ang 1-7, stimulated by MLT and cannabinoids, and inhibited by IL-17 and ET-1. Then, the simple detection of Ang 1-7 blood concentrations could constitute the main simple and synthetic laboratory parameter of the status of health. If future clinical investigations would confirm the pharmacological possibilities of Ang 1-7 in the treatment of most human systemic diseases,^[60] we could term Ang 1-7 as angioliberine from the word “libertas,” since it could contribute to make humans as potentially free from all systemic diseases, as well as from age-related problems themselves.

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