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Review Article

Angiotensin 1-7 as the Possible Universal Panacea of Human Systemic Diseases and Potentially the Best Anti-Aging Molecule of Human Body

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Abstract

The recent advances in the immunobiological knowledges have shown that the immune system is not involved in the only defence against infections and tumours, but also in the regulation of cardiovascular, endocrine, and nervous functions. Moreover, the activity of the immune system mainly depends on the cytokine network. However, most cytokines play an inflammatory action, with a consequent unbalance between inflammatory and anti-inflammatory responses. Then, the prevalent inflammatory action of cytokines is counterbalanced by an anti-inflammatory neuroendocrine central system, mainly mediated by the pineal gland, cannabinoid system, and ACE2-angiotensin 1-7 (Ang 1-7). In fact, the pineal hormone melatonin (MLT), the cannabinoid agents, and Ang 1-7, produced by the enzymatic activity of ACE2 on angiotensin II (Ang II), have appeared to exert an anti-inflammatory activity due to the inhibition of the secretion of several inflammatory cytokines. Moreover, their anti-inflammatory activity is constantly associated with an antitumoral action, by constituting a fundamental anti-inflammatory anticancer functional system. One of the main connections between cytokine network and neuroendocrine system would be IL-17, which has appeared to inhibit Ang 1-7 secretion and to stimulate that of Ang II, and whose secretion may be inhibited by MLT, cannabinoids and Ang 1-7 itself. Most human systemic inflammatory diseases have appeared to present an endogenous Ang 1-7 deficiency. In addition, aging itself is characterized by a progressive decline in the secretion of both pineal hormone MLT and Ang 1-7. Therefore, because of their anti-inflammatory anticancer activity, the progressive decline in MLT and Ang1-7 production may explain age-related increase in the incidence of tumours and other systemic pathologies. Moreover, Ang 1-7 deficiency has been shown to be associated with a concomitant enhanced production of Ang II, which exerts hypertensive, inflammatory, protumoral, pro-thrombotic and profibrotic effects, being responsible for several biological damages. Then, a substitutive treatment with MLT and Ang 1-7 might opposite age-related human diseases and counteract aging itself. Both MLT and Ang 1-7 have appeared to exert anti-aging antioxidant anti-inflammatory effects. However, the anti-aging biological properties of Ang 1-7 would be superior to those of MLT itself, since MLT may only slow down aging mechanisms, while Ang 1-7 could also regenerate the human body by reversing the atherosclerotic and fibrotic processes, which are responsible for the progressive organ failure.

Keywords: ACE2; Aging; Angiotensin 1-7; Anti-aging; Cytokine network; Inflammation; Melatonin; Pineal gland

Introduction

The possibility not only to treat the different human pathologies, but also to enhance the status of health and to prolong the survival time was a dream until the discovery more than 40 years ago of the fundamental role of the pineal gland in opposing age-related processes and to slow down their dynamics through the release of its most investigated indole hormone, melatonin (MLT) [1], which has appeared to play an essential function in modulating the biological systems in relation to the universal energetic conditions, namely the light/dark circadian rhythm [2], by representing the aging-clock of human body [1]. However, until few years ago the possibility to prolong the duration of life was attributed to the only pineal gland because of its capacity of counteracting free radical production-induced DNA damage and the occurrence of both tumours and cardiovascular disorders [3,4] through the release of MLT and other indoles. In addition, it has been recently discovered the existence of another fundamental potential anti-aging molecule, the angiotensin 1-7 (Ang 1-7), probably most potent than MLT itself because of its ability not only to slow down the aging processes, but also to regenerate the biological system by mainly acting on the endothelial cells to induce anti-sclerotic effects [5,6]. Ang 1-7 is the product of the enzymatic activity of ACE2 on angiotensin II (Ang II) after the transformation of angiotensinogen into Ang II induced by ACE. Ang 1-7 and Ang II are characterized by opposite effects on the cardiovascular system, since Ang II exerts hypertensive and cardio-hypertrophic effects, whereas

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Ang 1-7 plays hypotensive and cardioprotective actions. Moreover, both Ang II and Ang 1-7 have appeared to influence most biological functions with opposite effects. In fact, Ang II induces hypertensive, cardiac hypertrophic, inflammatory, protumoral, pro-thrombotic, neuroinflammatory, and pro-fibrotic effects, whereas Ang 1-7 exerts hypotensive, cardioprotective, anti-tumoral, anti-inflammatory, neurotrophic, anti-thrombotic, and anti-fibrotic effects [5,6]. ACE and ACE2 receptors are widely expressed on several cell types, namely on endothelial cells themselves. By synthetising, MLT plays its bioprotective effects by primarily acting on the immune cells, which have appeared to express MLT receptors [7,8], while Ang 1-7 would play its regenerative properties by directly acting on endothelial cells, whose characteristics may influence the physiopathological processes. Then, because of their fundamental anti-inflammatory and anti-tumor role, the clinical evaluation of the pineal endocrine activity and of the ACE2-Ang 1-7 axis function would have to be included within the common routine laboratory analyses to better define the status of health and to better understand the physiopathology of all human chronic systemic diseases. Moreover, it has been demonstrated that pineal gland and ACE-ACE2 system, which would constitute the two major regenerative biological systems, are connected by several reciprocal interactions, since MLT has appeared to inhibit ACE expression and stimulate that of ACE2 [9]. Therefore, ACE-ACE2 system would be under a pineal regulatory control. In addition, pineal itself contains an ACE-ACE2 system, which regulates the pineal endocrine function [10].

Pineal and Angiotensin 1-7 Deficiency-Related Human Diseases

Until now, the clinical investigation of the pineal endocrine activity has been substantially limited to the evaluation of its most known hormone, the indole MLT, whose secretion is characterized by a light/dark circadian rhythm, with high levels during the dark phase of the day and low during the light period [2]. Moreover, MLT secretion has appeared to change during the life and to dramatically decline with the pubertal development [11]. In fact, the decrease in the nocturnal levels of MLT would constitute the first endocrine sign of the sexual development, which precedes the occurrence of LH peaks during the night [11]. Finally, after the onset of puberty, MLT progressively declines with age until the disappearance of its circadian rhythm, with, however, important individual variations [12]. A diminished MLT endogenous secretion with a loss of its light/dark rhythm has been documented in all human system diseases, including advanced tumours [13], autoimmune pathologies [14], brain and cardiac ischemic diseases [15], and neurodegenerative and neuropsychiatric disorders [16]. Then, because of its anti-inflammatory, anti-tumor and antioxidant activities, the progressive decline in MLT secretion could contribute to the pathogenesis of human chronic systemic diseases and to their clinical evolution. Obviously, the evaluation of the other pineal indole hormones, namely the 5-methoxytryptamine [17], and beta-carbolines [18], the most known of them is the pinealine, will be necessary to better define the pineal function in the human physiology. As far as ACE-ACE2 system, its functionless may be investigated by simply detecting the blood levels of the products of the enzymatic activity of both ACE and ACE2, respectively consisting of Ang II and Ang 1-7. Therefore, Ang II-to-Ang 1-7 ratio could constitute a synthetic biomarker to define the in vivo functionless of ACE-ACE2 system. As well as shown for MLT, human systemic inflammatory and ischemic diseases have been also found to be characterized by a concomitant decline in the endogenous production of Ang 1-7, due to a diminished ACE2 expression with respect to that of ACE [19,20]. In fact, abnormally low blood levels of Ang 1-7 in association with a concomitant increase in those of Ang II have been documented in cardiovascular disorders [21], advanced neoplasms [22], autoimmune diseases [23], neurodegenerative pathologies [24], and metabolic syndrome [25]. Because of its hypotensive activity and its cardioprotective regenerative effects, Ang 1-7 could become one of the main drugs in the treatment of cardiac and vascular dysfunctions [21]. Ang 1-7 has been proven to be effective also in the treatment of pulmonary arterial hypertension. The efficacy of Ang 1-7 in the therapy of metabolic syndrome is due to its inhibitory action on adipocyte-related enhanced production of inflammatory cytokines, which may allow to the insulin resistance and to alterations in lipid metabolism [25]. Moreover, it has been shown that there is an ACE-ACE2 system also at brain level, and that a diminished expression of ACE2 with a consequent Ang 1-7 deficiency may promote both brain neurodegenerative and ischemic disorders [24]. Aging itself is characterized by a diminished Ang 1-7 secretion [5,6,19,20]. This evidence is not surprising by considering that Ang 1-7 exerts hypotensive, cardioprotective, anti-tumor, immunomodulating, neurotrophic effects [5,6], and may prevent the occurrence of insulin resistance [25]. Therefore, the diminished endogenous production of MLT and Ang 1-7 induced by pineal and ACE2 deficiencies could represent the main common pathologic mechanism, which characterizes the overall human inflammatory diseases, irrespectively of their clinical features. This statement is justified by the fact that all human diseases are characterized by an enhanced inflammatory status. Then, because of the fundamental anti-inflammatory role of ACE2-Ang 1-7 axis and the pineal gland either directly or through its connection with cannabinoid system and oxytocin [26], MLT and Ang 1-7 deficiencies would allow a chronic inflammatory status, which represents the common mechanism of human systemic diseases. The importance of the anti-inflammatory action of MLT and Ang 1-7 is furtherly remarked by the fact that most cytokines of the cytokine network are provided by inflammatory activity. Then, the control of the biological inflammatory response is physiologically firstly realized by a neuroendocrine control, mainly mediated by the pineal gland and ACE2-Ang 1-7 axis, rather than through cytokine network itself. Therefore, systemic disease-related inflammatory status could not directly be due to a primary immune cell dysfunction, but at least in part on an altered neuroendocrine regulation of the immunoinflammatory response. The main connection between neuroendocrine system and cytokine network would be played by IL-17, mainly released from Th17 lymphocytes, which has been proven to inhibit ACE2 expression and the consequent Ang 1-7 production [27], and whose secretion is inhibited by both MLT [28] and Ang 1-7 [29]. IL-17 has appeared to induce direct cardiovascular alterations, including ischemic and thrombotic disorders [30]. Then, MLT and Ang 1-7-induced inhibition of IL-17 secretion could represent one of the main mechanisms responsible for the protective biological properties of both MLT and Ang 1-7 themselves. Finally, it has been shown that the progressive increase in the endogenous production of IL-17 would constitute one of the main aging-related changes in the immune functionless [31], with a consequent predisposition to both

cancer and autoimmunity because of the promoting role of IL-17 on both cancer progression and autoimmune processes [32].

The Immunobiological Properties of Angiotensin 1-7

The endogenous production of Ang 1-7 is the end-result of multiple mechanisms involving several organs. The first step consists of a liver production of angiotensinogen, which is transformed into angiotensin I by renin produced by renal juxta-glomerular cells. Angiotensin I is transformed into Ang II by ACE. Finally, Ang II is degraded into Ang 1-7 by ACE2. ACE and ACE2 are mainly expressed on cell surface, even though they may be also present in the circulating blood. Ang 1-7 plays its biological effects by acting on Mas receptor [5,6]. ACE and ACE2 are widely expressed at tissue level, particularly by the endothelial system. Then, the main target of Ang II and Ang 1-7 actions would be endothelial system itself. All toxic and negative biological effects of Ang II, including vasoconstriction, cardiac hypertrophy, promotion of tumour growth through a stimulation of both cancer cell proliferation and angiogenesis, and activation of fibrotic and thrombotic processes, may be antagonized by Ang 1-7, which may also reverse the sclerotic and ischemic processes [5,6]. Moreover, Ang 1-7 may counteract Ang II-induced inflammation by inhibiting IL-17 secretion [29], which in contrast is stimulated by Ang II [27]. Finally, both MLT [1-4] and Ang 1-7 [21] have appeared to protect against irradiation injury [21].

The Biochemistry of Aging and the Fundamental Anti-Aging Role of Angiotensin 1-7

Today, it is known that aging is substantially characterized by a progressive loss of the biological circadian rhythm and an increase in the fibrotic processes involving the different organs of human body, including vessels, heart, liver, kidney, and lung [33]. From an endocrine point of view, the progressive decline in the pineal function would constitute the main endocrine failure of aging [1]. The decline in Ang 1-7 production constitutes another endocrine feature of aging [5,6]. Then, the human systemic diseases could be reinterpreted as an anticipation of aging processes themselves. Moreover, the different events characterizing the aging, including loss of biological rhythm, diminished nocturnal production of the pineal MLT, increased fibrotic and inflammatory processes, may be the effects of a common mechanism, which could consist of the decreased pineal endocrine activity [1,2]. In fact, because of the fundamental role of the pineal MLT in the regulation of the circadian biological rhythms [1,2], inflammatory status, cell proliferation, immune functions, as well as in promoting ACE2 expression and the consequent Ang 1-7 production, age-related biological changes could firstly be due to the progressive decline in the pineal function with age. On the other side, Ang 1-7 deficiency may explain age-related increase in the fibrotic processes, which have been shown to be induced by TGF-beta, because of the marked inhibitory action of Ang 1-7 on TGF-beta-induced fibrosis of the various organs of human body [34]. Moreover, because of the existence of an ACE-ACE2 system within the pineal gland, Ang 1-7 deficiency itself could furtherly amplify age-related pineal endocrine failure.

Disease as an Advance of Old Age

The main characteristics of old age can be summarized in these events: 1) progressive disappearance of biological rhythm (blood pressure, temperature and cortisol) as a consequence of the reduction of pineal endocrine activity 2) increase in the inflammatory state due to first of all to an increase in the production of IL-17, able to inhibit the activity of regulatory T lymphocytes with a consequent increase in autoimmune processes and to directly stimulate malignant growth, in turn as a consequence of a reduced activity of the various neuroendocrine systems provided of anti-inflammatory activity, i.e. the pineal gland, the endocannabinoid system and the ACE2-Angiotensin 1-7 system 3) increase in fibrotic processes affecting the various organs, due to increased production of TGF-beta as a consequence of a concomitant reduced activity of the anti-fibrotic system ACE2-Angiotensin 1-7. Now, being systemic diseases, both tumors and autoimmune diseases, characterized by an excessive inflammatory response (chronic in tumors and with acute episodes in auto-immunopathies), due in particular to an increased production of IL-17 and in the same way being the sclerosis of the blood vessels and of the various organs is due to TGF-beta, the main human systemic diseases can be imaginatively reinterpreted as an anticipation of old age, since the altered chemical processes in place are similar to each other. All systemic diseases, including tumors, autoimmune diseases, neurodegenerative diseases, atherosclerosis and metabolic syndrome, are due to an increased inflammatory state. Now, since the tissue involved in every inflammatory process affecting each organ is the endothelium itself, the modulation of the biological characters of the endothelium, aimed at stimulating the anti-inflammatory and anti-thrombotic properties of the endothelium compared to the inflammatory ones and pro-thrombotic, is the unifying principle of every possible type of treatment. Furthermore, by synthetically analyzing the entire human biology, we can identify three molecules with a particular toxicity, so much so that they represent real biological poisons, namely IL-17, endothelin-1 (ET-1) and angiotensin II (Ang II), being all provided with inflammatory and pro-tumor activity, and in the same way in polar form three molecules with not only reparative but regenerative capacity of the various cell systems, therefore real endogenous universal drugs, the hormone pineal-ic melatonin (MLT), cardiac atrial natriuretic peptide hormone (ANP) and Angiotensin 1-7 (Ang 1-7) as an enzyme product of ACE2. Ultimately old age is nothing more than a prevalence of pathogenic molecules over the therapeutic ones of the human body, that is to say of the Ang II on Ang 1-7, of the ET-1 on the ANP and of the IL-17 on the MLT, able to inhibit the secretion of IL-17 both directly and through its relationship with the endocannabinoid system, a powerful inhibitor of the secretion of IL-17, which constitutes the main mechanism of action of the cannabinoids themselves, both of the agonist cannabinoids and of the inhibitors of FAAH (Fatty Acid Amide Hydrolase), the enzyme that degrades cannabinoids, so that an increase in FAAH activity leads to an endo-cannabinoid defect. Almost all systemic diseases, beyond their main alteration, are characterized by a triple increase in IL-17, both in tumors and in autoimmune and atherosclerotic diseases, in ET-1, as in hypertension and in ischemic heart diseases and in the same neoplasms given the pro-tumor effect of ET-1, and Ang II, both in hypertension, heart disease and metabolic syndrome, but also in neoplasms, given the pro-tumor action of Ang II. from a laboratory point of view, despite the complexity of the molecular interactions in progress, the final result on the immune status is summarized by the ratio between lymphocytes and monocytes (LMR), in the norm above 2.1 and progressively lower due to a decrease in lymphocytes and an increase in monocytes in tumors advanced, in acute autoimmune diseases, in ischemic cardiovas-

cular diseases and in neurodegenerative diseases, for which an increase in LMR values may already be in itself considered a biological benefit and a sign of therapeutic efficacy. A control of the processes of old age can then be achieved simply by correcting the imbalance between the two chemical lines of Death, i.e., IL-17, ET-1, Ang II, and of Life, i.e., MLT, ANP and Ang 1-7, restoring the primacy of the Life Line. The secretion of ANP is stimulated by both MLT and Ang 1-7, so as a preventive scheme of old age, in the sense not only of slowing down but of regeneration, it is sufficient to administer low doses of Ang 1-7 in the morning (0-5 mg) and MLT at night (10 mg), Ang 1-7 to counteract the action of Ang II and inhibit IL-17, MLT, to which a possible cannabinoid agent can be associated, to inhibit IL-17 and ET-1.

Conclusions

Inflammation is the common mechanism responsible for the development of a systemic disease. Therefore, the control of the inflammatory response may be effective in the treatment of all inflammation-related human pathologies. Moreover, human systemic inflammatory diseases, including cancer, autoimmunity, neurodegenerative pathologies, metabolic syndrome, and aging itself have been shown to present a diminished pineal secretion of MLT and ACE2-induced Ang 1-7 production, which play a fundamental anti-inflammatory action. Then, according to the knowledges available up to now, at least from a theoretical point of view, all human systemic diseases and age-related pathologies may be counteracted and prevented by a chronic substitutive treatment with MLT plus Ang 1-7, also because of their complete lack of biological toxicities, even though at high doses [2,5,6]. Several other endogenous molecules, including the other pineal indole and beta-carboline hormones [17,18,26] and neurohormones such as TRH [35], may display anti-aging properties, but at present the association between Ang 1-7 during the morning and MLT during the night represents the most simple, non-toxic, non-expensive neuroimmune regimen to counteract the aging processes to enhance the happiness of the

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