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A Review on the Neuroendocrine Regulation of the Endothelial Cells

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ABSTRACT

Today, it is known that inflammation represents the common mechanism of human systemic diseases, including cancer and autoimmunity. Obviously, the endothelial system is involved in all inflammatory processes. Then, the control of the endothelial functions could constitute a new medical strategy to treat several pathological conditions, including ischemic and thrombotic events. Moreover, in addition to the action of angiogenic and anti-angiogenic factors, the endothelial system has been proven to be physiologically under a double control, represent by the cytokine network and the neuroendocrine system. Most cytokines have appeared to exert angiogenic and inflammatory effects, which are balanced by an anti-angiogenic and an anti-inflammatory action exerted by the pineal hormone melatonin (MLT), cannabinoid agents, and the product of ACE2, the angiotensin 1-7 (Ang 1-7). Then, a neuroendocrine approach with MLT, cannabinoids and Ang 1-7 could constitute a new way in the treatment of endothelial alterations and angiogenesis.

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Introduction

It is known that the inflammatory response essentially depends on the interactions occurring between immune cells and endothelial cells in influencing the characteristics of the endothelial system, mainly its permeability and coagulant properties [1]. Moreover, it is known that the biological characteristics of the endothelial cells are under a regulatory control, mainly exerted by the cytokine network through the secretion of its inflammatory and anti-inflammatory cytokines [2]. Finally, it has been proven that the cytokine network is under a physiological neuroendocrine regulation, mainly played by the opioid system the cannabinoid system and the pineal gland [3-5]. In more detail, the immune functions are stimulated by the pineal-cannabinoid functional axis, whereas they are regulated in an inhibitory manner by the opioid system and corticosteroid hormones [3-8].

In addition, it has been recently documented the existence of another fundamental system involved in the control of the endothelial functions, consisting of ACE-ACE2 system [9-11]. Moreover, it has been shown that the products of their enzymatic activity, represented by angiotensin II (Ang II) for ACE, and Angiotensin 1-7 (Ang 1-7), the so-called angio-liberin, may exert opposite effects on the endothelial system, since Ang II has been proven to play inflammatory, angiogenic, and pro-thrombotic effects, whereas Ang 1-7 exerts anti-inflammatory, anti-angiogenic, and anti-thrombotic activities [9-11]. ACE and ACE2 are widely expressed by most cell types, particularly by the same endothelial cells, then by the whole human body through its vascularization [9-11,12].

Therefore, because of the involvement of the endothelial system in all inflammatory processes and in the pathogenesis of the human systemic diseases, including cancer and autoimmune pathologies, it is fundamental to investigate the biological properties of endothelial cells, their cytokine and neuroendocrine regulation, and their involvement in the different inflammatory diseases [13,14]. Not only, but the investigation of endothelial cells would have at least to include the mechanisms responsible for the neo-angiogenic function, their coagulation properties, and their fibrotic processes. By summarizing, the most important endogenous molecules involved in the inhibition of endothelial-related inflammation are represented by the pineal hormones, such as melatonin (MLT), which is the most studied pineal hormone the endogenous cannabinoids ang And 1-7 [4,15,16,9-12].

Unfortunately, most studies have investigated separately the actions of these vascular protector molecules. In contrast, in vivo they are connected by several interactions and reciprocal promoting effects. In fact, MLT secretion and pineal activity have appeared to be under a stimulatory cannabinoid regulatory control [17]. Moreover, both MLT and cannabinoids have appeared to promote ACE2 expression and Ang 1-7 production, which in turn has been proven to promote cannabinoid receptor expression [18,4,16,19]. Therefore, the administration of each single agent, including MLT, cannabinoids and Ang 1-7, could promote the production of the other vascular protector molecules.

The Endothelial Regulation by the Cardiovascular System

The cardiovascular system shows a self-regulatory mechanism played by the same endocrine-like activity of hearth and endothelial cells, mainly due to the release of atrial natriuretic peptide (ANP) and endothelin-1 (ET-1) which are provided by opposite effects

[20,21]. ET-1 is potentially produced by all endothelial cells and endocardial cells, while ANP is produced by the only heart. ET-1 plays hypertensive, cardiotoxic hypertrophic, thrombotic, inflammatory, angiogenic, and pro-tumoral effects. On the contrary, ANP exerts hypotensive, cardioprotective, anti-inflammatory, anti-angiogenic, and anti-tumoral activities. Moreover, the activity of ET-1 is connected to vasopressin secretion, whereas ANP acts in connection with the neurohypophyseal hormone oxytocin, which has also appeared to play cardioprotective and cardio-regenerative effects [22]. Finally, ET-1 has appeared to stimulate IL-17 secretion and to inhibit ACE2 expression, with a consequent decline in blood levels of Ang 1-7, which in turn would inhibit IL-17 production, by constituting a double feedback mechanism [23,24,14].

The Effects of Interleukin-17 on The Vascular System

Today, it is known that there are at least two generation sites of the inflammatory response, consisting of the macrophage system through the release of several inflammatory cytokines, including IL-1beta, IL-6, IL-8, and TNF-alpha, and the Th17 lymphocytes, which release IL-17. All inflammatory cytokines tend to induce vascular damage and vessel sclerosis, but the maximal vascular alterations would be induced by IL-17, which has been proven to enhance the procoagulant properties of the endothelial cells and to determine cardiac dysfunctions [25]. Moreover, the action of IL-17 is linked to that of ET-1, since ET-1 has been proven to promote IL-17 secretion [23]. Finally, IL-17 has appeared to modulate ACE-ACE2 system by stimulating ACE expression and inhibiting that of ACE2, with a following decline in Ang 1-7 endogenous production and its deficiency [26]. The inhibitory action of both MLT and cannabinoids on IL-17 secretion would represent the main mechanism responsible for their anti-inflammatory action [2,4,5]. MLT has also appeared to inhibit ET-1 secretion and promote that of ANP, which plays a reciprocal stimulatory action on MLT secretion [6].

The Immunoendocrine Regulation of Angiogenesis

The angiogenesis is commonly investigated only in relation to the action of angiogenic factors, the most biologically active of them is VEGF [27]. However, the angiogenic processes are under a complex regulation, constituted of angiogenic factors, hormones, cytokines, and neuroactive agents. Then, the event of angiogenesis would represent the end-result of a central neuroendocrine and immune regulation. The main stimulus for the onset of angiogenesis is hypoxia itself, which induces the production of hypoxia-inducible factor-1 (HIF-1), and the following VEGF secretion. Most inflammatory cytokines, including IL-6, TNF-alpha, and primarily IL-17 itself, stimulate the angiogenesis [25].

Angiogenesis is also stimulated by some hormones, including vasopressin and GH [28,29]. Finally, ET-1 has also been proven to exert an important angiogenic action [21]. In contrast, the angiogenesis, namely tumor neo-angiogenesis, is inhibited by the pineal MLT, the cannabinoid agents, ANP and oxytocin [30,4,20,22]. Then, in addition to the direct administration of anti-angiogenic factor monoclonal antibodies, the angiogenic processes could also be controlled by a neuroendocrine approach, according to the physiological anti-angiogenic pineal-cannabinoid-oxytocin-ANP functional axis.

The Immune and Hematologic Effects of Angiotensin II and Angiotensin 1-7

In addition to their effects on endothelial characteristics, Ang II and Ang 1-7 may also influence the hematopoietic activity, then cell content of blood. As well as for their cardiovascular effects, Ang II and Ang 1-7 would play opposite effects on hematopoietic differentiation and immune cells function [15-19]. Even though the results are still preliminary, it seems that Ang 1-7 may promote lymphocyte differentiation, and inhibit monocyte generation and macrophage system activation. On the contrary, Ang II stimulates the macrophage system, and suppresses lymphocyte functions, with the following inflammatory and immunosuppressive effects [31].

As far as the influence on T lymphocyte subsets, Ang II has appeared to stimulate Th17 lymphocytes and IL-17 production, which is responsible for the onset of autoimmune diseases, and inhibit regulatory T lymphocyte activity [14]. Then, because of the opposition in the biological effects of Ang II and Ang 1-7, it is probable that Ang 1-7 may inhibit Th17 cell function and IL-17 secretion, which could justify its employment in the treatment of autoimmune disease, since autoimmunity would be related to an ACE2 reduced expression [9-12]. Platelet production would be also promoted by Ang 1-7 [31]. Since MLT may also promote lymphocyte and platelet generation this evidence would furtherly confirm the connection occurring between MLT and Ang 1-7 [5,15].

The Effect of Angiotensin II and Angiotensin 1-7 on Coagulation Processes

Even though the complex molecular mechanisms need to be better investigated and defined, it has been shown that Ang II plays a major procoagulant action by inducing an endothelial damage, whereas Ang 1-7 has appeared to exert a clear anti-thrombotic activity with a following potential therapeutic efficacy also in the treatment of Covid19 disease since the thromboembolic events may represent one of the major causes of death in association with respiratory distress-induced lung failure [15-19,32]. In fact, according to the recent discoveries, would constitute a disease consisting of an acute and severe Ang 1-7 deficiency [32]. ACE-ACE2 system includes various other active peptides, such as angiotensin 1-5, angiotensin 1-9, and angiotensin IV, consisting of the peptide 3-8 of the octapeptide Ang II but at present the most investigated and promising molecule would be Ang 1-7 itself [9-12,33].

Conclusions

The already demonstrated existence of a central neuroimmune regulatory control of all biological functions, such as inflammatory response, endothelial cell characteristics, and immune reactions would have to allow a profound renovation in the clinical practices, founded on a systemic action rather than on single appr: oaches on the different biological functions, including inflammatory response, angiogenesis, and immune functions, since in vivo the biological response is only one into three different aspects, consisting of inflammatory, angiogenic, and immune responses. The clinical use of pineal hormones, cannabinoids, and Ang 1-7 would represent the most simple, non-toxic, and non-expensive ways. The complex neuroendocrine regulation of ACE-ACE2 system is illustrated in Figure 1.

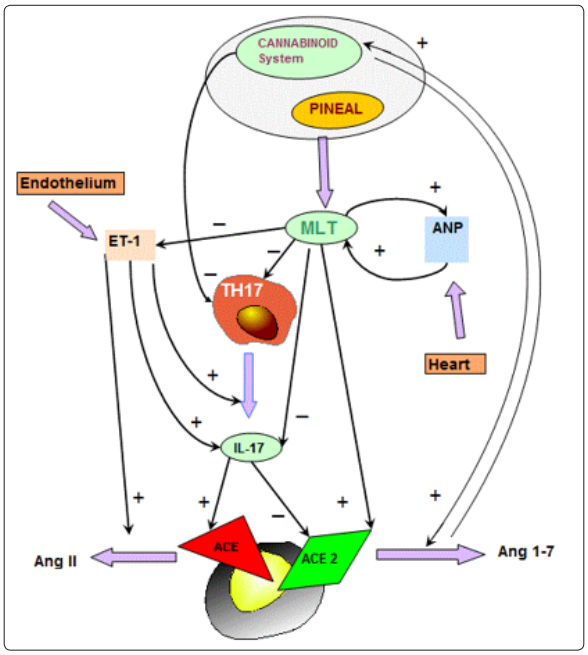

Figure 1: Neuroendocrine regulation of the ACE – ACE2 system. (MLT: Melatonin; ANP: Natrial Natriuretic Peptide; ET-1: Endothelin-1; Ang II: Angiotensin II; Ang 1-7: Angiotensin 1-7)

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