The modulation of the endocannabinoid system in the treatment of cancer and other systemic human diseases

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Abstract

Despite cancer is at present considered as a systemic disease, in the clinical management of patients the neoplastic disease is often up to now generally considered and treated as a loco-regional pathology. The systemic nature of cancer is documented by the evidence of the fundamental role of the immune system in the control of tumor onset and dissemination. However, it must be taken into consideration that the in-vivo immune responses are under a physiological neuroendocrine control, namely played by brain opioid and cannabinoid systems. The endogenous cannabinoid system has been proven to exert a fundamental anti-inflammatory action. Then, since the chronic inflammatory status has appeared to promote cancer growth and dissemination, it could be clinically important to evaluate the functional status of the endogenous cannabinoid system in cancer patients. The endogenous cannabinoids, the most important of them are anandamide and 2-arachidonyl glycerol, are destroyed by the fatty acid amide hydrolase (FAAH) enzyme, whose levels are inversely correlated to those of the endogenous cannabinoids. Moreover, it has been observed that the evidence of abnormally high blood concentrations of FAAH, which reflect low levels of cannabinoids, has appeared to predict a poor prognosis in cancer patients. Therefore, the determination of FAAH blood levels would have to be included within the laboratory analyses of cancer patients in an attempt to synthetically evaluate their neuroimmunomodulatory status. Finally, the inhibition of FAAH synthesis and activity could represent a new possible approach in the bio-immunotherapy of human tumors.

Introduction

It is known that the endocannabinoid system exerts a fundamental role in the regulation of most biological functions by inducing metabolic, immunomodulatory and psychochemical effects, and in particular it has been shown that brain cannabinoid system plays an essential role in both pleasure perception and pain control [1]. Moreover, the recent discoveries in the area of the Psycho-neuro-endocrino-immunology (PNEI) have demonstrated that immune system-mediated systemic human diseases, including cancer and autoimmunity, would be due to an altered neuroendocrine regulation of the immune responses rather than to a primary alteration of immune cell functions themselves [2]. Despite its great complexity, the psycho-neuroendocrine regulation of the immunity has appeared to mainly depend on two major brain interneuronal systems, consisting of the cannabinoid [1] and the opioid system [3,4]. There are three essential opioid receptors, mu-, delta- and kappa receptors, and two main cannabinoid receptors, CB1 and CB2. The psychedelic psychotropic effect of cannabinoids is mediated by the activation of the CB1 receptor, whereas CB2 receptor, which is namely expressed by the immune cells, is involved in the modulatory effects of cannabinoids on the immuno-inflammatory biological response [1]. The two main endocannabinoids are represented by the arachidonyl-ethanol-amide (AEA), the so-called anandamide, and the 2-arachidonyl-glycerol (2-AG) [1]. The main enzyme involved in cannabinoid degradation is the fatty acid amide hydrolase (FAAH) [1]. The importance of the neuroimmunomodulatory processes exerted by brain opioid and cannabinoid systems is confirmed by the evidence of a possible enhanced or diminished activity of both brain opioid and cannabinoid systems in the pathogenesis of cancer, as well as other systemic immune-mediated diseases, including autoimmunopathologies and cardiovascular diseases. In particular, it has been shown that stress-induced promoting effect on tumor development has appeared to be mediated by an enhanced opioid system activity, since the administration of mu-receptor opioidantagonists may abrogate the influence of stress on tumor progression [4]. Moreover, it is known that the progressive lack of pleasure perception, the so-called anaedonia, represents one of the main and most frequent cancer progression-related symptoms. Then, because of the fundamental role of endocannabinoids in the perception of pleasure [1], the evidence of cancer-related anaedonia would suggest that tumor diffusion may be characterized by a progressive failure of brain cannabinoid function, with consequent alterations in immune system function. On the contrary, other diseases, such as the acute schizofrenia, has been proven to be associated with an enhanced brain cannabinoid system activation [5]. Obviously, before analyzing the modulatory effects of the endocannabinoid system and most in general of the neuroendocrine system, it has to be synthetically considered the functionless of the immune system and the cytokine network, since the influence of the neuroendocrine system on the immunity is mainly mediated by its influence on the cytokine network.

The functional structure of the immune system and the anticancer immunity

Despite its great complexity, the immune system is mainly constituted by two major cell systems, the old or innate immunity, mainly mediated by the granulo-monocyte system and NK cells, and the new or aquired immunity, mainly mediated by the lymphocyte system. The immune status is the end results of two major dynamics, represented by the immunostimulation and the immunosuppression, which are respectively mainly exerted by the lymphocyte and the macrophage systems. Within the lymphocyte system, the only regulatory T lymphocytes (T reg) (CD4+CD25+) exert an immunosuppressive anti-inflammatory action, and their generation has appeared to be under a macrophage stimulatory regulation. The connection between innate and acquired immunity is namely represented by the dendritic cells (DC), mainly through the release of IL-12 [6], which would represent the main link between old and new immunity, then between macrophage and lymphocyte systems, whose interactions are responsible for the overall types of immune response. The immune response is mainly activated by T helper-1 (TH1) (CD4+) lymphocytes through the release of IL-2 and gamma-IFN. TH1-induced immune activation allows two different types of cytotoxic response, antigen-dependent and antigen-independent cytotoxicity, respectively mediated by cytotoxic T lymphocytes (CD8+) after IL-12 stimulation and NK cells after their IL-2-induced evolution into LAK cells [7]. Cancer would be characterized by a decline in TH1 and DC count and activity in association with an enhanced macrophage and T reg cell function. On the other side, the autoimmune diseases are characterized by a decline in T reg cell system activity, with following low levels of IL-10 and TGF-beta, in association with an enhanced activation of TH17 lymphocytes (CD4+CD17+) and a consequent enhanced secretion of IL-17, which would constitute the main inflammatory cytokine involved in the pathogenesis of the autoimmune disorders. From a PNEI point of view, the cytokine alterations occurring in cancer, autoimmunity, cardiovascular diseases, and neurodegenerative pathologies could be due at least at the beginning of the pathology to an altered neuroendocrine control of cytokine network itself [2]. Then, the cytokine network could be influenced by acting on its psychoneuroendocrine regulation, which is mainly exerted by the opioid and cannabinoid systems, rather than to directly act on the various cytokine secretions. IL-12, in addition to its importance in the relations between innate and acquired immunity, would also play an essential role in the interactions between cannabinoid system and immunity [8], since IL-12 has been proven to inhibit FAAH activity, with a consequent increase in cannabinoid endogenous content, whereas IL-10 may stimulate FAAH, with a consequent diminished cannabinoid concentration. Then, the immune system may modulate the function of brain cannabinoid system by simply influencing FAAH synthesis and activity, by enhancing the activity of the cannabinoid system through the release of IL-12, and by decreasing its function through that of IL-10, respectively responsible for the immunoactivation or the immunosuppression. The secretion of IL-10, which exerts an anti-inflammatory immunosuppressive activity [2], is stimulated by the opioid system [3], which is active in stress, pain and depressive conditions, whereas the cannabinoid system is involved in pleasure and spiritual sensitivity conditions [1]. Then, these evidences would explain the immunosuppressive effects of stress and the immunostimulatory one of the pleasure, and the spiritual expansion of mind.

The neuroendocrine regulation of the immune system

The central nervous and the neuroendocrine systems influence the immune system by acting on the cytokine network and modulating cytokine secretions [1-5]. The neuroimmunomodulation is namely exerted by the two major brain interneuronal systems, represented by the opioid and cannabinoid systems. The mu-opioid agonists, such as morphine and beta-endorphin, play an immunosuppressive activity [3,4] by stimulating the secretion of IL-10 and TGF-beta, which inhibit the antitumor immunity [9], as well that of IL-17 [10], and by inhibiting that of the two main anticancer cytokines in humans, IL-2 and IL-12. More controversial are the immunomodulating effects of delta-and kappa-opioid agonists. On the same way, contradictory results have been reported about the immune effects of cannabinoids, since both stimulatory and inhibitory effects on IL-2 , IL-12, TGF-beta and IL-10 secretions have been observed, whereas most studies have confirmed the inhibitory action of cannabinoids on TNF-alpha and IL-17 secretions, which would explain their anti-cachectic and anti-inflammatory activities, respectively. The controversial results concerning the immune effects of cannabinoids would depend by the fact that they are mediated by the interactions between brain cannabinoid system and pineal gland [11], whose essential role in the modulation of the immune system has been well proven.

Clinical applications of the knowledge of the cannabinoid system

Clinical investigation of the endocannabinoid system

The endocannabinoid system may be clinically investigated by measuring the blood and liquoral concentrations of the two major endocannabinoid agents, consisting of AEA and 2-AG, or probably in a more simple and synthetic manner by determining the blood concentrations of the enzyme responsible for cannabinoid degradation and metabolism, the FAAH, whose enhanced production may allow a decline in the endogenous cannabinoid content [1]. On the contrary, a diminished synthesis of FAAH would allow an increased cannabinod system activation. The acute phase of schizophrenia would be associated with an enhanced cannabinoid activity, as confirmed by the evidence of abnormally high levels of AEA in association with low concentrations of FAAH [5]. Because of the well demonstrated anticancer properties of cannabinoid agonists [1], due to several mechanisms, including direct anti-proliferative cytotoxic effect, anti-angiogenic activity, and inhibitory action on macrophage-mediated immunosuppressive inflammatory events, the evidence of a schizophrenia-related cannabinoid system hyperactivation could explain the low frequency of cancer in schizophrenic patients [5]. On the contrary, an enhanced production of FAAH, with a consequent decline in cannabinoid system activity, could constitute a risk factor for cancer onset and development, because of the fundamental role of the endocannabinoid system in the natural biological resistance against cancer in the optimal psycho-neuroendocrino-immune status of health [1,11]. In fact, it has been demonstrated that tumor expression of FAAH is associated with a more biological malignancy and a poor prognosis in some tumor histotypes, including prostate cancer [12]. Then, the inhibition of FAAH synthesis, with a consequent increase in cannabinoid concentrations, could constitute a new possible biological approach in the treatment of tumors. Moreover, by considering that FAAH activation may induce an enhanced inflammatory response by suppressing the anti-inflammatory action of the endogenous cannabinoids and a consequent enhanced production of inflammatory cytokines, such as IL-1beta, IL-6, TNF-alpha and IL-17, the inhibition of FAAH synthesis and activity could exert therapeutic benefits also in the cure of cardiovascular diseases [13], and neurodegenerative disorders [14], which are also determined at least in part by an enhanced inflammatory response. Psychiatric diseases themselves are

also characterized by the evidence of an enhanced inflammatory status, as suggested by the possible evidence of high levels of inflammatory cytokines, namely IL-6 [15]. By summarizing, FAAH inhibitors or stimulators could be successfully employed in the treatment of human diseases, respectively characterized by an abnormally low or abnormally high function of the endocannabinoid system. As far as the cardiovascular system is concerned, the endocannabinoid system may influence heart and endothelium functions by the simple regulation of FAAH synthesis, whose increase would allow an enhanced production of inflammatory cytokines, which negatively influence both cardiac and nervous activities. Then, from a therapeutic point of view, the inhibition of FAAH activity to enhance brain cannabinoid functionis more important than its eventual stimulation to reduce brain cannabinoid content. Another important enzyme in the control of the cardiovascular system, which is connected to FAAH through several neuroendocrine interactions, is neprilysin (NEP), also called enkephalinase, a zinc-dependent membrane peptidase involved in the metabolism and degradation of several vasoactive peptides, including atrial natriuretic peptide (ANP), endothelin-1 (ET-1), and enkephalins [15]. NEP synthesis and activity may influence the cardiovascular functions by affecting the inflammatory response, whose end-result would depend on its major degradation of molecules, suchas ANP [16] or ET-1 [17], which are provided by anti-inflammatory immunostimulatory or inflammatory and immunosuppressive effects, respectively. The inhibition of NEP activity has appeared to enhance the vasodilator effect of the angiotensin II-type 1 receptor antagonists, such as valsartan, as well as their inhibitory action on ET-1 secretion [17].

Therapeutic implications

At present, the most simple manner to modulate the functionless of the endogenous cannabinoid system, whose alterations have been proven to be involved in cancer, autoimmunity, neuropsychiatric and cardiovascular diseases, is represented by the control of FAAH synthesis and activity. Several FAAH inhibitors have been elaborated [18], and the pineal hormone MLT has appeared to cooperate with FAAH inhibitors to counteract FAAH activity with a following further increase in brain cannabinoid content [19]. On the contrary, leptin, a chemokine produced by the adipocytes provided by a stimulatory effect on inflammatory cytokine production, may stimulate FAAH activity, with a following decline in brain endocannabinoid content, which allows a decline in appetite and food intake [20]. Most of FAAH inhibitors are profen or phenyl-alkyl-sulfonyl-fluoride derivatives, and preliminary clinical studies seem to suggest the potential therapeutic efficacy of FAAH inhibitors in several human diseases, including cancer, depression, and cardiovascular pathologies, all characterized by a chronic enhanced inflammatory status, due at least in part to an endocannabinoid system deficiency. By summarizing, the measurement of FAAH blood concentrations is already sufficient to investigate the inflammatory status of patients, since the evidence of abnormally high levels of FAAH reflects and allows an enhanced inflammatory response because of the decline in the endogenous cannabinoid content and function induced by the high levels of FAAH. Then, it is possible to modulate the inflammatory status of patients by simply acting on FAAH synthesis and activity. Moreover, since the hyperactivation of the inflammatory response may be considered as the common pathological mechanism involved in the main human systemic diseases, including cancer and autoimmune diseases, the control of the inflammatory status by cannabinoids agents provided by anti-inflammatory effects would represent a fundamental point in the treatment of the already now untreatable human systemic pathologies.

Conclusions

It is already known that the cannabinoid agents may play a fundamental role in the treatment of most advanced cancer-related symptoms, including cachexia, anorexia, anaedonia, vomiting and pain. In addition to these therapeutic properties, at present it has to be also taken into consideration the important role of the cannabinoid system in the systemic control of the inflammatory response, and the functional status of the cannabinoid system may be clinically established by the simple determination of FAAH levels, whose concentrations are inversely correlated to those of the endogenous cannabinoids. Then, the determination of FAAH levels would have to be included within the routinary laboratory analyses of cancer patients, since the evidence of high FAH levels has been proven to be associated with an enhanced inflammatory response and with a suppression of the anticancer immunity [2], then with a worse prognosis in terms of both response to therapy and survival time.

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