Journal Of Clinical Neurology, Neurosurgery And Spine

Special Issue Article "Cannabinoid"

Review Article

Possible Mechanisms Responsible for Stress Predisposition to Cancer or to Autoimmune Diseases

Paolo Lissoni*, Giusy Messina, Roberto Trampetti, Andrea Sassola, Enrica Porta, Giorgio Porro and Giuseppe Di Fede

Institute of Biological Medicine, Milan, Italy

ARTICLE INFO

Received Date: February 14, 2022
Accepted Date: March 17, 2022
Published Date: March 18, 2022

KEYWORDS

Cannabinoid system
Melatonin
Neuroimmunomodulation
Opioid system
Pineal gland
Stress

Citation for this article: Paolo Lissoni, Giusy Messina, Roberto Trampetti, Andrea Sassola, Enrica Porta, Giorgio Porro and Giuseppe Di Fede. Possible Mechanisms Responsible for Stress Predisposition to Cancer or to Autoimmune Diseases. Journal Of Clinical Neurology, Neurosurgery And Spine. 2022; 4(1):124

Corresponding author:
Paolo Lissoni,
Institute of Biological Medicine, Milan, Italy,
Email: paolo.lissoni@gmx.com

ABSTRACT

Today it is known that the enhanced brain opioid system activity represent the major neurochemical variation occurring in stress conditions. Moreover, it has been shown that a chronic opioid hyperactivation may suppress the anticancer immunity, and promote cancer development. On the contrary, the influence of stress on the autoimmune processes is more complex, since the mu-opioid agonists may stimulate both TGF-beta and IL-17 secretion, which respectively may counteract or promote the onset of the autoimmune diseases. The in vivo preferential effects of opioids on TGF-beta or IL-17 secretions could depend on the functional status of brain cannabinoid system, which has been found to inhibit IL-17 secretion. Then, the neurochemical corrections of the major stress-related neuroendocrine and cytokine alterations could constitute a new physiological approach in the treatment of stress-related disorders.

INTRODUCTION

It is known that stress may predispose to both cancer and autoimmune diseases [1-3]. Then, the physiopathological question is to establish whether the promoting influence of stress on the development both cancer and autoimmune diseases, which are characterized by the opposite immune reactivity, may depend on the type of stress or on the different immunobiological response. Moreover, despite the complexity of its mechanisms, it has been proven that stress is mainly characterized by en enhanced brain opioid system activity, since it has been demonstrated that the concomitant administration of an opioid antagonist, such as naloxone o naltrexone (NTX), may abrogate stress-induced immune alterations [4]. Moreover, stress has appeared to be characterized by an enhanced secretion of vasopressin, the so called Antidiuretic Hormone (ADH), by the neurohypophysis, as well as by an increased CRH production at hypothalamic level, with a following activation of the Hypothalamic-Pituitary-Adrenal (HPA) axis and the sympathetic system [5,6]. The mu-opioid agonists, such as beta-endorphin and morphine, have been proven to induce immunosuppression by inhibiting TH1 lymphocyte and dendritic cell functions and by stimulating regulatory T lymphocyte (T reg) system [7,8], with a consequent decreased secretion of IL-2 and IL-12 in association with an enhanced production of TGF-beta . Being IL-2 and IL-12 the main antitumor cytokines in humans [9,10], and TGF-beta the main endogenous

immunosuppressive factor [11], these evidences may explain their promoting action of stress on tumor development and progression.

Cancer-stress relationships

Today it is known that the antitumor immunity is mainly stimulated by IL-2 and IL-12 [9,10], whereas it is inhibited by the anti-inflammatory cytokines TGF-beta and IL-10 [11], as well as by most inflammatory cytokines, including IL-6, IL-1beta and TNF-alpha [12]. TGF-beta and IL-10 have appeared top counteract the antitumor immunity by inhibiting IL-2 secretion from TH1 lymphocytes and that of IL-12 from the dendritic cells [11], while IL-6 may inhibit IL-2-induced transformation of NK cells into LAK cells [9]. NK cells are not active against fresh human cancer cells, since they have been shown to exert their cytotoxic acivity only against artificial laboratory tumor cell lines. On the contrary, LAK cells are able to destroy fresh human cancer cells collected from the same cancer patients [9], by representing the main cells responsible for antigen-independent anticancer cytotoxicity. IL-2 plays an anticancer action by stimulating LAK cell generation [9], while IL-12 exerts its anticancer activity by promoting IL-2 secretion [10], and by inhibiting TGF-beta release [13]. Therefore, stress-related promotion of tumor development may be simply explained as a consequence of a chronic suppression of the antitumor immunity induced by the enhanced brain opioid activity occurring during stress conditions [4]. The inhibition of IL-2 [7,8] and IL-12 scretions induced by the mu-opioid agonists in association with a stimulation of TGF-beta and IL-10 release is already sufficient to explain stress-induced immunosuppression of the anticancer immmunity [4-8].

Autoimmunity-stress relationships

According to the more recent immune discoveries, at present it is known that the autoimmune diseases are mainly due to an enhanced production of IL-17 from TH17 lymphocytes [14]. IL-17 promotes the develpment of autoimmune processes by namely inhibiting T reg cell functions, with a following diminished production of the immunosuppressive factor TGF-beta [15]. Moreover, IL-17 secretion is also induced by IL-1 beta, and reciprocally it may stimulate IL-1beta and IL-6 release [15], with a following activation of the macrophage system. The influence of stress on the development of autoimmune processes is more complex to be explained, because of the controversial effects of the mu-opioid agonists on IL-17 and TGF-beta production. In fact, the mu-opioid agonists have appeared to stimulate the secretion of both TGF-beta and IL-17 [16]. The preferential stimulatory effects of mu-opioid agonists on TGF-beta or on IL-17 release may explain at least in part the mechanisms by which stress may either stimulate or counteract the occurrence of autoimmune processes. In more detail, a preferential stimulatory action of mu-opioid agonists on IL-17 secretion may predispose to the development of autoimmune mechanisms, because of the inhibitory effect of IL-17 on TGF-beta secretion [15], whereas a preferential stimulation of TGF-beta secretion could protect against the onset of autoimmune processes [17]. The preferential stimulatory effect of the mu-opioid agonists on IL-17 or TGF-beta secretion could depend at least in part on the functional status of the other fundamental brain neuromodulatory system, the brain cannabinoid system [18], since the endogenous cannabinoid agonists, including arachidonyl-ethanol-amide and 2-arachidonyl-glycerol, have been proven to inhibit IL-17 secretion [18,19], whereas they have no relevant effect on that of TGF-beta. Then, the influence of stress-related enhanced brain opioid tone on the autoimmune dynamics could depend on the concomitant functional status of brain cannabinoid system. In the presence of a normal cannabinoid function, stress-related effects of the opioid system could preferentially allow an enhanced TGF-beta secretion, because of the inhibitory effect of cannabinoids on IL-17 release, whereas in the presence of a concomitant reduced brain cannabinoid function, the enhanced opioid activity would preferentially allow an enhanced release of IL-17 and promote the onset of autoimmune processes. A diminished brain cannabinoid tone has been demonstrated in the presence of anaedonia [18], which consists of a diminished pleasure perception. On the contrary, irrespectively of the preferential effect of stress on TGF-beta or IL-17 secretions, stress constantly represents a promoting factor for tumor development, since both TGF-beta and IL-17 may exert stimulatory effects on tumor onset and growth. In fact, TGF-beta may promote tumor growth by suppressing the antitumor activity, while IL-17 may exert a protumoral action by directly stimulating cancer cell proliferation [20].

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HOW TO INVESTIGATE STRESS-INDUCED IMMUNE ALTERATIONS?

According to the recent advances in the knowldedge of the immune physiology, the main target of stress is not the endocrine system, but the immune system, since the biological variations occurring in stress conditions are fundamentally the consequence of an altered neurondocrine control of the immune functions. Then, the question is how to clinically analyze the immune status of patients in a synthetic and less expensive manner, by taking into consideration that few clinical examinations are not sufficient, and that many laboratory analyses risk to allow controversial results among the great number of possibile immune and neurondocrine parameters. At present, an adequate clinical investigation of the interactions occurring between immune and neuroendocrine systems either in basal, or stress conditions, would have at least to include the evaluation of the circadian rhythm of both cortisol and the pineal hormone melatonin (MLT), the Lymphocyte-to-Monocyte Ratio (LMR), the TH1-to-T reg ratio (TH1/T reg), and blood levels of IL-6, IL-17, IL-2, IL-12, and TGF-beta. This synthetic proposal of laboratory examinations is justified by the fact that IL-1 beta, TNF-alpha, and IL-8 tend to present the same behavior than that of IL-6, gamma-IFN secretion is related to that of IL-2, and IL-10 is generally released in association with IL-10.

Stress-Induced Neuroendorine and Cardiac Parameters

In normal conditions, cortisol levels are higher during the morning and lower in the afternoon and evening, whereas the pineal hormone MLT is higher during the dark period of the day and lower during the light phase, with a following generation of a light/dark circadian rhythm [21]. The progressive loss of the light/dark MLT rhythm has been observed in most human systemic diseases, including advanced cancer, autoimmune diseases, cardiovascular disorders, and neurodegenerative pathologies [21]. The lack of cortisol decline during the afternoon and the absence of MLT increase during the night may be considered as a sign of desynchronization, which consists of the loss of the connections to the environmental conditions and the universal energetic variations. Stress is also characterized by changes in the neurohypophyseal function, with an enhanced secretion of ADH, and a diminished release of oxytocin (OT). Moreover, both ADH and OT have been shown to influence the cardiac endocrine activity, since ADH has appeared to stimulate the secretion of endothelin-1 (ET-1), which is also released from the endothelial cells of the cardiovascular system [22]. On the contrary, OT has appeared to stimulate the release of Atrial Natriuretic Peptide (ANP) [22,23]. Because of the anti-inflammatory, antitumor, immunostimulatory, anti-angiogenic, and cardioprotective activities of ANP [24], and in an opposite way the inflammatory, pro-tumoral, immunosuppressive and angiogenic actions of ET-1 [25], as well as its involvement in the induction of heart hypertrophy, the influence of stress on the cardiac endocrine activity would play a fundamental role to explain the toxic effect of stress on the human biology. Then, the evaluation of ADH-to-OT ratio, as well as of ANP-to-ET-1 could constitute an important clinical parameter to quantity the intensity of the influence of stress in each single patient. Finally, it has to be remarked that the functionless of brain opioid system cannot be adequately evaluated without taking into consideration its connection with brain cannabinoid system [18,19], was main neuroimmune activity would consist of the inhibition of IL-17 secretions and that of the other main inflammatory cytokines, including IL-6 and TNF-alpha. The function of the endogenous cannabinoid system may be clinically investigated by the simple measurement of the Fatty Acid Amide Hydrolase (FAAH), the enzyme involved in cannabinoid metabolism and destruction [18,19]. Then, the evidence of abnormally high blood levels of FAAH would reflect an endogenous cannabinoid deficiency [26], which has been proven to characterize most human systemic diseases, including metastatic neoplasms and cardiovascular diseases.

Stress-induced immune parameters

Actually, an adequate clinical immune evaluation would require the determination of the main lymphocyte subsets, the main inflammatory and anti-inflammatory cytokines, and the main immunosuppressive protumoral and anticancer immunostimulatory cytokines. In any case, since the immune functionless is substantially the end-result of the interactions occurring between lymphocyte and monocyte-macrophage systems, the simple Lymphocyte-to-Monocyte Ratio (LMR) has appeared to reflect the whole immune status, since the evidence of abnormally low values of LMR has been proven to predict a poor prognosis in both cancer and cardiac ischemic

disease [27,28], and reflect an enhanced T reg lymphocyte activity [29]. Moreover, despite the complexity of lymphocyte subpopulations, the function of T lymphocyte system is fundamentally the end-result of the interactions between TH1 and T reg cells, corresponding to TH1/T reg ratio [30], since they represent the main cells responsible for the immunoactivation or immunosuppression, respectively. Finally, as far as cytokine measurement is concerned, it could be sufficient to evaluate blood levels of IL-6 and IL-17, the main cytokines respectively responsible for macrophage or TH17-dependent inflammation, those of TGF-beta as the main immunosuppressive agent, and those of IL-2 and IL-12, which are the main antitumor cytokines in humans [9,10], and may exert both inflammatory and pro-inflammatory effects, depending on the different biological conditions. Then, to evaluate the immune status of patients from a clinical point of view, in a very synthetic way it could be sufficient the simple detection of LMR values, which may be associated to that of TH1/T reg ratio to better define the status of T reg cell system. For a more complete clinical investigation, it could be sufficient the evaluation of IL-6, IL-17, TGF-beta, IL-2 and IL-12 blood concentrations.

Influence of stress on neuroimmune interactions

The main connections between neuroendocrine and immune systems are consisting of the stimulatory effect of the inflammatory cytokines, including IL-6 and TNF-alpha, on the HPA axis, with a following increase in cortisol blood levels and a possible progressive loss of its circadian secretion, and on the other side of the stimulatory action of IL-2 and IL-12 on brain cannabinoid system-pineal functional axis [31], since IL-12 has been shown to inhibit FAAH activity [32], with a following increase in brain cannabinoid tone, and low-dose IL-2 has appeared to restablish the physiological light/dark rhythm of the pineal hormone MLT in cancer patients [33].

POSSIBLE NEW THERAPEUTIC STRATEGIES TO CONTROL STRESS-INDUCED IMMUNE ALTERATIONS

The pineal hormone MLT has appeared to constitute one of the main anti-stress endogenous factors [34], since it may inhibit the activation of the sympathetic system, modulate the HPA axis, and regulate brain opioid system through its connection with brain cannabinoid system [35]. MLT has also appeared to counteract stress-induced immunosuppression, and exert an anti-inflammatory function [36]. Finally, the control by MLT of anxiety-related stress may be furtherly amplified by a concomitant administration of cannabidiol (CBD), the anti-inflammatory non-psychotropic agent of Cannabis [18,19,37]. Obvioulsy, being the hyper-activity of brain mu-opioid system the main stress-related neurochemical variation, the most simple strategy to counteract stress-related increased brain opioid activity would have to consist of the block of the opioid system through the administration of a long-acting mu-opioid antagonist, such as NTX, as already observed in experimental conditions [4]. In fact, NTX has been proven to reduces T reg cell system activity [38]. At present, however, the results with NTX in humans are still controversial, and no defined conclusion may be proposed, in particular when it is administered in association with cannabinoid agents, since some effects induced by cannabinoids are mediated by the same opioid system [18,19], which could be abrogated by the concomitant administration of an opioid antagonist. Another strategy to counteract stress-related hyperactivation of brain opiod system and the same action of stress, namely on the immune system and on the cardiac function, may consist of OT administration, since OT has been shown to be inhibited by the mu-opioidagonists [39]. Opioid-induced inhibition of OT secretion occurring during stress may explain at least in part some stress-related psychological profiles, including anxiety, diminished perception of pleasure, and a decline in the cognitive functions. This statement is justified by the fact that OT has appeared to play a fundamental role in the modulation of anxiety, mood, social recognition, affective relationships, sexual behavior, and cognitive function, because of its stimulatory role on mirror neuron system, as well as cannabinoids and the pineal hormone MLT [40].

CONCLUSION

The recent advances in the area of Psycho-Neuro-Endocrino-Immunology (PNEI) have allowed the possibility to control the negative effects of stress on both psychospiritual life and immune system through a physiological -neurochemical strategy by simply correcting the main immune and neuroendocrine alterations occurring under stress conditions, when they become excessive and detrimental, in an attempt to establish the neuroimmunochemical status of health.

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