The Significant Role of the Sympathetic Nervous System in Hospitalization and Death of Patients With COVID-19: Psycho-Neuroendocrine-Immune Aspect of Stress

Farideh Zafari Zangeneh[1], Maryam Sarmast Shoushtari[2]

[1] Vali-e-Asr Reproductive Health Research Center, Family Health Research Institute, Tehran University of Medical Sciences, Tehran, Iran

[2] Department of Bio-Medical Engineering, Chemical and Environmental Engineering, Faculty of Engineering, University Putra Malaysia, 43400 Serdang, Selangor, Malaysia

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Abstract- The primary immune responses to CoV-19 are inter-individual variability against this virus. Studies on the neuro-immune system demonstrate that interactions in these communication pathways can be a reason for several psychiatric disorders and immune-mediated diseases. Stress-related behaviors are significant in the psycho-immune interactions, and even stress-related factors such as socioeconomic status can also play a vital role in these interactions. A literature review on the topic was carried out, and 150 articles were included. Catecholamine and glucocorticoids are stress neurohormones. Noradrenaline as signaling molecules, through macrophages, can be an essential stimulus for cytokine secretion. Glucocorticoids, by both pro-and anti-inflammatory roles in specific conditions, can inhibit the elevation of the inflammatory response by inhibiting the pro-inflammatory macrophage activation and also enhance the anti-inflammatory activity in monocyte/macrophage populations the further eliminate. Stress with this flawed amplification feedback system can disrupt immune homeostasis (cytokine storm) in the patient with COVID-19. This investigation showed that there is a strong link between psycho-neuroendocrine-immune axis organizations against respiratory viral infections during the COVID-19 epidemic. The stress cascade must be responsible for meeting the body's hemostatic challenges in the necessary physiological and metabolic interactions. The motivation of the stress system leads to behavioral/physical variations that are strangely consistent in their qualitative presentation. These variations must be generally adaptive and increase the chances of the individual's survival. In coronavirus respiratory disease, identifying people with acute/chronic psychosocial stress is of particular importance for providing prompt care as soon as possible, as scheduling intervention appears to be an essential factor in reducing stress and hospitalization rate in the intensive care unit (ICU).

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Introduction

It took a long for immunologists to understand that the immune system is not a self-regulation system and that its function is carefully associated with the nervous system. These associations are significant at different organizational levels. At the limited or local level, there are strong signals for the activation (production/usage) of immune factors by the central nervous system (CNS) which this process leads to the production of neuroendocrine mediators. This association in the short-range interactions between peripheral nerve endings and immune cells causes neuro-immune system to respond (1).

Corresponding Author: F. Zafari Zangeneh
Vali-e-Asr Reproductive Health Research Center, Family Health Research Institute, Tehran University of Medical Sciences, Tehran, Iran
Tel: +98 2166581616, Fax: +98 2166581658, E-mail address: Zangeneh14@gmail.com

The history of research on neuro-immune interactions shows that alteration in these communication pathways between two systems (immune and nervous systems) can cause several psychiatric disorders and immune-mediated diseases. One of the most critical pathways in routine matter is the modulation of immune responses by stimulation of the stress pathways. Two main stress pathways that were studied are the sympathetic nervous system (SNS) and the hypothalamic-pituitary-adrenal (HPA) axis (2). In this review, we first focus on essential points related to SNS function in the inflammation process. The second part is for trying to understand the regulatory machinery in inflammatory disease by referring to the findings of neuroendocrine-immune regulation.

Coronavirus

In the last two decades, after severe acute respiratory syndrome (SARS) and the Middle East respiratory syndrome (MERS), COVID-19 as coronavirus disease is the third respiratory infection that was firstly defined in Asia. The first report on COVID-19 was in December 2019 in Wuhan, China. Coronavirus (nCoV) of Wuhan 2020 belongs to the Beta coronavirus.

Coronavirus and central nervous system (CNS)

Viral infections have damaging influences on neurological functions and even cause severe neurological injury. Coronavirus, particularly severe acute respiratory syndrome, can show neurotropic properties and even causes neurological diseases. Coronavirus has been detected in the brain and cerebrospinal fluid of patients. Patients in the critical phase are more neurological symptoms than patients with mild to moderate disease. The autopsy reports have shown brain tissue edema and limited neuronal disintegration in dead patients. For the first time, Beijing Ditan Hospital, on March 4, 2020, reported a viral encephalitis case caused by the novel coronavirus (3). COVID-19 could reason for infectious, toxic encephalopathy with early manifestations without attacking the brain itself, and it can cause CNS damage and neurological symptoms (4). Pneumonia, typically in hypoxic patients, develops to type 1 respiratory failure, with a low carbon dioxide (CO2) level and high respiratory rate. Nevertheless, brain failure typically leads to type 2 respiratory failures, with low oxygen/ high CO2 and decreased respiratory rate. Virus neuro invasion would cause respiratory failure; thereby, the virus should be detected in the cerebrospinal fluid of these patients (5).

Coronavirus: Crosstalk between CNS and immune system

Interference between the CNS and the immune system is classified as an antigen-independent process such as ontogeny, cell turnover, migration, and sensitivity to signal processes. These processes (antigen-independent) are very significant in assigning the intensity and duration of the immune response, enabling the defense mechanisms of the host to be quite regulated (6). Non-focal neurological manifestations, including encephalopathy with severe respiratory, metabolic, and immune disorders, can be occurred during critical illness without viral neuroinvasion (7).

Neuropathogenic reports in humans and animal models indicate several CNS lesions, including neuronal necrosis, demyelination, and meningoencephalitis. Olfactory abnormalities as a reflection of peripheral nasopharyngeal are not CNS dysfunction (8). These neurologic manifestations alternated from justly particular symptoms (loss of smell or taste senses, myopathy, and stroke) to rather non-particular symptoms (headache, depressed level of consciousness, dizziness, or seizure). Mao *et al*., reported in 2020 that the neurological symptoms of COVID-19, such as stroke, ataxia, seizure, and depressed level of consciousness, were more common in the more severe disease (30.2% in non-severe patients and 45.5% in severe patients) (9). These signs are genuinely neurologic. The olfactory and blood-brain barrier (BBB) can be two routes for viruses entering into CNS (10).

Olfactory route

The virus is internalized through endocytosis in nerve terminals, and the retrograde form can be transmitted virus to spread trans-synoptically to other brain areas (11). The loss of smell sense without congestion is a common neurological sign of COVID-19. ACE2 and TMPRSS2 are localized in the epithelial cells (sustentacular cells) (12), together with neuronal involvement (13).

Blood-brain barrier (BBB) route

This barrier is a standard route for the entry of the virus into the brain. Bryce *et al*., 2020 reported that angiotensin-converting enzyme2 (ACE-2) immunoreactivity was detected in the autopsy of the brain vessels in a COVID-19 patient who died with thrombotic microangiopathy by the multiple ischemic infarcts (14). This entry is possible through other potent SARS-CoV-2 receptors, more widely expressed in cerebral vasculature (15).

Disrupt the blood-brain-barrier (BBB) by cytokines

COVID-19-associated cytokines include interleukin-6 (IL-6), IL-1β, IL-17, and tumor necrosis factor (TNF) which disrupts the BBB to facilitate virus entry (16,17).

Coronavirus and cytokines/inflammation

The classification of cytokinesis included three different groups: 1) pro-inflammatory cytokines for assisting in starting the immune response (IL-1, IL-6, and TNF); 2) anti-inflammatory cytokines for damping the immune response (IL-4, IL-10, and IL-3); and 3) hematopoietic cytokines for stimulating the differentiation blood cells (IL-3, IL-5, and G-CSF) (18). Studies show that IL-6 has an essential role in the crosstalk between cytokines and CNS.

Interleukin 6 (IL-6)

IL-6 was cloned in 1986 (19), and its family involves ten members. IL-6 is a pleiotropic cytokine produced in response to tissue damage and infections (20). IL-6 levels in these conditions can increase a thousand-fold and help coordinate the response to impaired tissue homeostasis (21). Interleukin-6 is a multifunctional cytokine that plays an essential role in the interaction between the immune and nervous systems. The SNS known as the neuroimmune has bidirectional interaction with the immune system. This interaction is necessary for normal neural function, growth, and disease. The critical function is to maintain and protect tissue homeostasis in neuro-immune interactions. The sympathetic innervation of immune cells in the various lymphoid organs is one arm of this interaction (22). However, no information is available about the effect of immune factors on the central neural circuits for regulating sympathetic nerve discharge (SND). The bursting pattern of SND affects various physiological functions, including the regulation and of generating differential patterns in SNS efferent outflow, synchronizing or desynchronizing of the activity SNS in different targets, and its regulation. The alteration of the SND pattern has a consistent feature for SNS regulation of targets in response to physiological conditions. So, a change in the efferent pattern can be an essential regulatory factor in responding to the target organ. Helwing *et al*., in 2008 showed that elevations of IL-6 levels in the cerebral spinal fluid (CSF) could alter the efferent SND pattern and suggested that in pathophysiological conditions, this elevation of IL-6 in CSF may contribute to the sympathetic dysregulation (23).

IL-6 plays a vital role in many central physiological responses, including; hypothalamic expression of corticotrophin-releasing factor (CRF), activation of the HPA axis, fever, and memory constitution. IL-6 levels in CSF are elevated in response to the CNS in trauma, inflammation, central degenerative disease (Alzheimer), meningitis, and autoimmune diseases (24). However, the communication between CNS and IL-6 is not direct, and the other regulatory mechanisms must play a significant role here. Numerous reports of evidence obtained in the laboratory from the last two decades show that the brain can significantly modulate IL-6 production in the periphery. This evidence shows that: a) The stimulus of central inflammatory can efficiently induce peripheral IL-6; b) central opioid is one of the most effective modulators of peripheral IL-6, and c) SNS represents an inhibitory pathway to peripheral IL-6 (25); d) interaction between SNS and opioid system generally results in decreasing SNS tone (26), and opioids are immunosuppressed (27).

Peripheral IL-6 and CNS

IL-6 as a vital cytokine controls the transition from innate to adaptive immunity. Preliminary studies have shown IL-6 expression and its production during modeling encephalitis in mice in the CSF of patients with acute viral infections and viral meningitis (28). In the CNS, pro-inflammatory cytokines are produced by microglia and astrocyte neurons. These proteins have a direct effect on neurotransmission, for example, increasing pain transmission (29). Even though IL-6 is often associated with inflammatory and pathological conditions, it is a significant factor in the normal function of the brain. Therefore, IL-6 is involved as a bodyweight regulator via food intake and energy expenditure (30), as a stimulator for the pituitary-adrenal axis (31), induces fever (32), and is for the control the body temperature after stroke (33). IL-6 orchestrates transmission from the innate immune response to the adaptive immune response and inhibits neutrophils, monocytes, and T-cells for late inflammatory action. It can induce astrogliosis and angiogenesis required for tissue demodulation and recovery, and chronic IL-6 may also cause significant brain damage (34).

What factors are involved in the association between peripheral IL-6 and the CNS? (Microglia cells)

Cytokines, which are a significant part of the modulators of the immune and nervous systems, can be released by microglia. IL-6 also shows several special effects on the glial and endothelial cells.

Glial cells guarantee the usual construction and

function of the brain. Glial cells are subdivided into macro and microglia, with many neural functions, including development, function, and immune response (35). Macroglia are substantial neurons, like astrocytes and oligodendrocytes, which have essential roles in brain's homeostasis. Macroglia permit the neurons to mature and migrate, and they also insulate and care for neurons and axons during the growing time and on the environmental conditions (36). However, microglia cells are mesoderm-derived immune cells that attack the CNS during initial development. In physiologic/pathologic conditions, they can organize the competent scavenger cells. Therefore, there may be a hypothesis that glial cells can be non-neuronal cells with specific functions and markers (37).

Microglial cells and immune system (source and target for cytokines)

Microglia is a monitoring cell for environmental health that can respond to signs of the homeostatic disorder via its supportive and protective plans for defense mechanisms with particular immune responses (38). Microglia is a significant regulator of the innate defense of the immune system. Microglia is an assistant for the beginning immune responses and affects it. On the other hand, neurons are sensitive to cytokine signals of microglial, so extreme or continued activation could considerably contribute to acute and chronic neuropathology, and disruption of the microglial cytokine production can be a cause of neurotoxicity. Most neurological diseases are associated mainly with glial activation (39) because microglia can express IL- 6 receptors, IL- 1, and TNFα. IL-6, as a pro-inflammatory cytokine, triggers and regulates the inflammatory response in the acute phase and limits the prevalence of infectious agents (40). Infectious agents (prion protein) and the other viral/bacterial cell wall components cause the activation of macrophage/microglia. There may even be confusion in the immune system caused by certain virus-encoding cytokine structures, receptor homologs, or cytokine-binding proteins. Some cytokines can participate in endocrine-endocrine neurotransmission by modulating neural activity in the mature CNS because immune cells can synthesize and secrete some immunomodulatory hormones that regulate the immune system to reduce or block any intensified inflammatory response. For example, macrophages (41) and lymphocytes (42) can produce catecholamine (noradrenaline/adrenaline) and endogenous opioid peptides (43).

Astrocyte cells and immune system

Astrocytes are the vital constituent of neural circuits in vivo. Astrocytes arrangement very related links; they are widely joined via cellular connections (gap junctions). Astrocytes are well-positioned to increase the effects of diffuse the projections of neuromodulators. The highly branched process of astrocytes serves two essential purposes: 1) increase the interaction with the low concentrations of neurotransmitters, and 2) protect nerve cells through increasing diffusion distance from varicosities to neuronal membranes (44). Astrocytes are vital regulators for the cerebral immune system (innate and adaptive) responses, and their activity is dependent on the timing and context that may worsen inflammatory response and tissue damage or advance the immunosuppression process and tissue repair during neuroinflammation or neuro infection (45). These findings confirm that astrocytes have a vital role in the regulation of neuron homeostasis and neuroprotection. Astrocytes are the most abundant cerebral cell type, which can help in the neuroprotective activity by the mechanical holding of the nerve tissue and maintaining BBB homeostasis. This is a critical mechanical role for astrocytes in regulating neuroglia communication by secretion of neurotrophic factors, neuromodulation of neurotransmitter releasing and its metabolism, control of the cerebral blood flow, and maintaining tissue homeostasis in CNS by protecting the protection of pathogens in both neuroinflammation and neuroprotection settings (46).

IL-6 and neuro-inflammatory response

IL-6 as a neurotrophic factor is vital for the differentiation of oligodendrocytes (47) and the retrieval of peripheral nerves (48). The cellular effects of IL-6 exert via two pathways: the anti-inflammatory pathway through membrane binding with the IL-6 receptor, which expresses on the microglia and astrocyte for bacterial defense in classical signaling with activating of the β-receptor glycoprotein 130 (gp130), and the other pathway is trans-signaling (49). Classical signaling is serious for anti-inflammatory signs in comparison to pro-inflammatory trans-signaling. The neurotoxic and neuroprotective function of microglia cells are associated with activated lipopolysaccharide (LPS), IFN-γ, or TNF-α in the classically activated pathway (M1), which has a critical role in pathogen defense by the production of pro-inflammatory cytokines including IL-1β, TNF-α, STAT3, IL-6, IL-12, IL-23, and reactive oxygen species (ROS), with the loss of neurons. Conversely, the other M2 anti-inflammatory phenotype

supports tissue remodeling/repair and angiogenesis by high releasing levels of anti-inflammatory cytokines, including IL-10, IL-4, IL-13, and TGF-β, and the low levels of pro-inflammatory cytokines (50). Emergent evidence shows that pro-inflammatory cytokines can modulate brain excitability by increasing seizure through upregulation of excitatory glutamatergic and downregulation of inhibitory GABAergic transmissions (51).

Numerous human and animal studies have shown that inflammatory cytokine IL-6 is associated with seasonal infections and severe H1N1A (H1N1pdm) influenza. Paquette *et al*., 2012 reported that there is an IL-6 level is a significant cytokine in the host response of humans, mice, and pigs versus H1N1pdm (52). Raised levels of IL-6 were associated with the severity of the disease in hospitalized patients. IL-6 could be a significant biomarker of the severity of the infection, but it cannot be an appropriate therapeutic target for the severe H1N1pdm infection (53). Hou *et al*., in 2014, showed that an extreme level of IL-6 produced by a viral infection could raise the IL-17 through pathogenic helper T cells. They suggested that IL-6 synergistically with IL-17 increases the expression of survival molecules to prolong serious mechanisms in the host defense in the virus-infected cells, which can control chronic viral infections, autoimmune diseases, and cancers (54). Walsh *et al*., suggested that adults needing hospitalization exhibited extensive virus shedding against raised levels of mucosal IL-6 (55). IL-6 in a meta-analysis including nine studies (total of 1426 patients) of COVID-19 showed that mean IL-6 levels were three times higher in severe COVID-19 compared, and IL-6 level was accompanied by the risk of mortality (56). Zheng *et al*., 2017 reported that the circulation levels of IL-6, TNF-α, and MCP-1 were higher in the patients with chronic obstructive pulmonary disease (COPD) by Influenza-A compared to the normal group (17).

From peripheral inflammatory signaling to the CNS (BBB)

Parasympathetic afferents primarily mediate the peripheral immune response, and cytokines can enter the brain directly through the BBB. Studies have shown that the movement of leukocytes from the BBB is primarily done during peripheral inflammation. This process should probably occur by activating the brain endothelium in the presence of pro-inflammatory messengers that increase endothelial cell expression, which is essential for cellular recruitment into tissues (57). The brain responds to peripheral signals; endothelial and perivascular cells synthesize prostaglandin E2 (58) by diffusion into the parenchyma for stimulation of temperature maintenance in the hypothalamus and fever (59) and stimulates adrenocorticotropic releasing hormone (ACTH) from the pituitary and secretion of corticosteroids from adrenal (60). Fever is a complicated signal for inflammatory and infective diseases produced by endogenous pyrogens (cytokines) and reaches areas of the hypothalamus. This occurs mainly by overproducing the cytokines or imbalance between cytokines and their inhibitors, such as severe and exploding infections and septic shock.

Neuroimmunomodulatory effects of CNS/immune system

There are multiple pathways for communication between CNS and immune system, including neural and non-neural. The nervous system regulates immune responses through bidirectional communication with the immune system. This communication can be done by multiple neuroanatomical pathways, hormonal routes, and molecular instruments (23).

CNS signaling on the immune system:

I. Hormonal pathways by neuroendocrine axes

1) The hypothalamic-growth-hormone (HGH) axis:

Growth hormone (GH) is mainly mediated by insulin-like growth factor-1 (IGF-1). GH and IGF-1 modulate the survival and proliferation of lymphoid cells (61). GH receptor is in a superfamily of cytokine receptors and therefore, it can express GH receptors. Thus, immune tissues produce GH as an autocrine/paracrine signaling pathway. GH as a cytokine can promote cell cycle growth of the lymphoid cells and regulate apoptosis (62). Throughout chronic stress, continuous HPA axis activation and excessive glucocorticoid production may limit hypothalamic–GH axis activity (63). Children with chronic inflammatory illness, for example, experience growth retardation. The GH level is elevated and then decreased throughout the primary phase of inflammatory reactions. This reduction is due to resistance to GH and IGF-1 caused by inflammation. In primarily IL-1α excites GH (64) but later prevents its secretion (65). This retardation and prevention of GH secretion in children and adults are due to changes in mitochondrial function. During aging, the effects of GH/IGF-1 are significant in the mitochondrial respiration and production of ATP. Other fundamental mitochondrial functions like calcium homeostasis, cellular replication, generating ROS, and

apoptosis play critical roles in the two processes, growing and aging. In aging mitochondrial dysfunction, GH/IGF-1 plays indirect effects on mitochondrial biogenesis (66).

2) The hypothalamic-pituitary-adrenal (HPA) axis:

The activation of the HPA axis and the release of hormones of the neuroendocrine-stress axis via neuronal pathways are required for maintaining internal homeostasis (67). Inflammation inhibits the effect of cytokines on the thyroid- releasing hormones (TRH) by preventing the secretion of thyroid stimulation hormones (TSH) (68). Although IL-1 can suppress TSH secretion (69), and also IL-2 can stimulate the pituitary–thyroid axis (70), the interaction of two axes, HPA and HPT is associated with the autonomic nervous system (ANS).

3) The hypothalamic-pituitary-gonadal (HPG) axis:

HPG and sex hormones (particular estrogen) have a significant role in the immune-regulatory mechanism. On the other, signaling the immune system in the brain includes cytokines and immune mediators (23).

4) The Hypothalamic-pituitary-thyroid (HPT) axis:

HPT axis has bidirectional communication with the immune system. It has an immunomodulatory effect by TRH, TSH, and the thyroid hormones T3/T4, which all have stimulatory effects on immune cells and cause to change immune system responses. Hypothyroidism is caused by a decrease in HPA axis reaction, while an increase in HPA axis response causes hyperthyroidism. The interaction of two axes, HPA and HPT, causes to change immune system responses (71). In the rat modeling of hyperthyroidism, administration of thyroxine induces the HPA axis activation, and it can be has a protective role against an inflammatory challenge (72). The hypothyroidism model also has been shown to cause a reduction in CRH gene expression (73). Findings from a study of 274 patients with SARS-CoV-2 showed that TSH and T3 concentrations were significantly lower than in recovered patients (72). Wei *et al*., 2007 reported that T3 and T4 concentrations in SARS-CoV-2 patients were considerably lower than in the control group, so the low level of T3 related to the severity of virus infection. During the acute phase, these reductions in blood T3 and T4 levels were 94 percent and 46 percent, respectively, in 48 patients, and 90 percent and 38 percent during the recovery phase (74). As a result, the SARS-CoV-2 data suggest that the thyroid gland and HPT axis are directly affected by this infection. In these axes, the cytokine-HPA interaction is a vital consideration for the maintenance of homeostasis in viral infection. The activation of the HPA axis is associated with the release of glucocorticoids (GC) via cytokines that have a critical role in shaping immune responses pattern during viral infection. GC has a significant role in the shape of a traffic-immune cell to the inflammation site and change in adaptive immune system responses through triggering a shift from cellular (Th1/inflammatory) to humoral (Th2/anti-inflammatory) type immune responses. In chronic inflammation, the production of local cytokines in the brain, the anterior pituitary, as a paracrine connection can increase and maintain HPA activity. Viral infection determines the kinetics and magnitude of stimulation in the HPA axis and then GC release (75). In the hypothyroidism model, it also has been shown to cause a reduction in CRH gene expression (73,76).

II. Neural pathways

Immunomodulation aspect of noradrenaline, opioids, and glucocorticoids

The autonomic nervous system (ANS) has an essential role in the short and long-term regulation of homeostasis and inflammation. The crosstalk between the SNS and inflammation with neuroendocrine-immune regulation causes them to interact with each other. SNS activation is an essential part of the usual fight and flight response. Evidence gathered over the past decades demonstrates the pivotal role of this and its neurotransmitters in regulating inflammation. The interaction between SNS and the immune system can firmly control inflammation if the transfer of local inflammatory mediators to the bloodstream triggers the activation of the brain's two main stress pathways, the HPA axis and the SNS. For example, interleukin (IL-1β) (51) or TNF is produced locally by innate immune cells because these cytokines are essential for this connection link between the immune system and CNS (57). Prass *et al*., in 2003 showed that sympathectomy reduces the infection rates through the SNS-mediated immunosuppression process (77). All neurotransmitters directly affect the immune cells, but Noradrenaline (NA) has an essential and significant role in this relation because SNS directly innervates lymphoid tissues and the releasing of NA from these nerve terminals (78). Grebe *et al*., in 2010, suggested that SNS plays a vital role in the innate autoimmune immunopathology and increases the probable advantage of alpha-receptor antagonist drugs for considering extremely pathogenic influenza1 virus infections (79). The multistep sequence leading to leukocyte migration is thought to be locally

regulated at the inflammatory site. The long-range signals of SNS by adrenergic nerves can regulate the rhythmic utilization of leukocytes in tissues (80).

Catecholamine-cytokine response

Noradrenaline (NA) is a significant local and systemic regulator for the immune system. This regulation is mediated by adrenergic signaling on immune cells through modulating inflammation by producing cytokines. Denervation of noradrenergic fibers in lymph nodes leads to amplification of inflammation (21). The signaling of β2-adrenergic receptors on the lymphocytes regulates cell traffic from lymphoid organs (81), and mice lacking β2-adrenoceptor (β2AR-/-mice) can maintain immune homeostasis (82). Lymphocyte β2-adrenoceptive stimulates CCR7-dependent retention signals, thus inhibiting the entrance of lymphocytes from lymph nodes into inflamed tissues and preventing lymphocyte migration (80). SNS activation is related to diseases, inhibition of (T cell helper) Th1-mediated inflammation and diminished $CD8^+$ T cell-mediated (adaptive immunity), and then shift to enhanced Th2 responses (83). For example, in multiple sclerosis, β2 adrenoceptors are greater than before in peripheral mononuclear cells (84) or in rheumatoid arthritis (RA) density, and the affinity of β2-adrenoceptors decreased in the peripheral mononuclear cells (CD8+ T cells and B cells) (85). In RA, SNS modulates inflammation for the synovial tissue, which is innervated by the sympathetic nerve fibers. Hence, there is a significant reduction in sympathetic nerve fibers in chronic RA conditions that can reduce its anti-inflammatory effects (86, 87). In cancer, SNS signaling damages the defense responses of the anti-cancer immune system and therefore accelerates and raises tumor cell invasion (88). Primary pro-inflammatory cytokines upregulation of IL-1β and TNF-α is modulated by IL-10 upregulation, which can reduce pro-inflammatory signaling (89). Studies show that catecholamine exactly inhibits IL-1 (90), IL-2 (91), IL-12 (92), TNF-α (93), IFN-γ (94) and increase the release of IL-10 (95), IL-6 (96) transforming growth factor-β (97) and IL-8 by the beta-adrenoceptor (98).

NA regulates pro-and anti-inflammatory cytokines by β_2-adrenoceptor. It reduces TNF-α expression and increases the production of anti-inflammatory IL-10 (99). In normal physiologic conditions, NA as the α/β-agonist decreases TNF-α and increases IL-10 expression in monocytes exposed to lipopolysaccharide (LPS) and other stimuli (100).

Opiates-cytokine response

Opiates have anti-inflammatory and analgesic effects in peripheral inflamed tissue without the central opioid side effects, including respiratory depression, sedation, and dependency (101). Wybran *et al*., 1979 showed the modulation role of opioid receptors on the human T lymphocytes (102), and then in 1988, Sibinga and Goldstein reported the expression of opioid receptors on immune system cells (103). Many recent studies have confirmed the presence of three opioid receptors in T cells. In T cells, the -receptor has been extensively studied. Morphine controls various facets of T cell function as an agonist of the μ-receptor. One of the impacts of opioid-induced immunological regulation is the balance of T-helper cells. Some opioids can cause interleukin-4 (IL-4) to be produced, which has an anti-inflammatory effect (104). Several studies have been conducted to investigate the acute effects of opioids in order to determine how morphine affects the immune system.

Nevertheless, chronic opioids seem to have a different result on the immune system response. For example, one-year intrathecal administration of morphine in patients who suffer from chronic nonmalignant pain showed an elevation of mRNA levels in μ-opioid receptor (MOR) in the T lymphocytes and B lymphocytes. Even upper levels were detected in patients treated with the co-administration of morphine/bupivacaine. After two years, this elevation in mRNA levels of MOR was confirmed in patients. The mechanism of this increase is unclear, but studies show that immune cells contain opioid peptides that can release it and accumulate in chronically inflamed tissue and acts as a cytokine through MOR up-regulation, which can be a reasonable interpretation (105). Met-enkephalin (MENK) as opioid growth factor (OGF) and leu-enkephalin are ligands for δreceptors of the endogenous opioid peptides. MENK alone or in combination with IL-2 or IFN-γ can cause the up-regulation of both $CD4^+$ T cell extension and expression of the CD4 molecule in-vivo/in-vitro, and it can raise the creation of $CD4^+$ T cells (106), and κ-opioid receptor (KOR) binds to dynorphin with a critical role in the regulation of T-cells (107). These studies showed that opioid receptors signaling with the immunomodulatory properties could control respiratory syncytial virus replication and thus can control disease severity (108).

Glucocorticoids-cytokine response

Glucocorticoids (GCs) inhibit cytokine expression-hyper inflammation in patients infected with COVID-19,

which causes too much cytokine, which can have lethal effects. Interestingly, an accruing body of indication now powerfully proposes that GCs have both pro-and anti-inflammatory roles in specific conditions. These two opposite properties are necessary for eliciting cellular responses to inflammatory stimuli as a protection mechanism for priming the immune cells to respond to the stressor and then return to normal homeostasis. Sickness behavior is generally termed for behavioral responses caused by brain's cytokine signals with activation of the HPA-axis and facilitated fever by prostaglandins, pain, and induction of a series of mood and behavioral patterns. Therefore, the GCs pro-inflammatory activity in the CNS can be the most manifest activity (109) because GCs inhibit the expression of cytokines. This is part of the in-vivo feedback system between inflammation-derived cytokines and CNS-adrenal-produced corticosteroids with the probable physiological relevance to balance parts of the host defense and anti-inflammatory systems of the body. GCs modulate cytokine expression by a combination of genomic mechanisms (110). Studies on the active human blood mononuclear cells have shown that glucocorticoids can strongly produce the cytokines IL-1β and TNF-α as well as immunomodulatory cytokines, including IL-2, IL-3, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12, Interferon-gamma (IFN-γ), and the Granulocyte-macrophage colony-stimulating factor (GM-CSF) (110). Brain's cytokines, such as IL-1, IL-6, and TNF-α, can stimulate the HPA axis. For example, IL-1 can stimulate CRH release from the hypothalamus by its gene expression in this nucleus, and then ACTH is released from the anterior pituitary (111). IL-6 (112) and TNF-α (113) can also stimulate ACTH release. An experimental model could induce arthritis by possibly lowering normal daily corticosterone levels in both Lewis and DA rats. After 7-21 days of adjuvant-induced arthritis, the circadian rhythm decreases with chronic activation of the HPA axis (114). This HPA-axis activation was due to amplified pulse frequency of secretion corticosterone in adjuvant-induced arthritis (115). In this condition, rats cannot respond to acute stress (noise) but can still respond to acute immunological stress (116). GC antagonist or adrenalectomy disrupts the disease process, resulting in death or disease situation in surviving animals (117,118). Thus, in the cytokine storm, adrenalectomy mice exposed to these pro-inflammatory stimuli die with responses such as shock (119).

In a viral infection, the primary pro-inflammatory cytokines (TNF-α, IL-1, and IL-6), and in the latter, T cell cytokines (IL-2 and IFN-γ) are stimulation factors for releasing GCs at the HPA axis. In this process, cytokines activate HPA, and the HPA axis plays a vital role in preventing and affecting immune responses. However, in the local production of cytokines at each area of the HPA axis, it may also enhance and maintain high HPA activity (hyperactivity) during chronic inflammation or in viral infection. Therefore, each area of the HPA axis covers a local cytokine network. Just as cytokines stimulate GC secretion and inflammatory responses, they can regulate the GC activity outcome.

COVID-19 and corticosteroid therapy

GCs, like adrenal cortex neuro-hormones, carry out many physiological functions that are vital for survival. In the clinic, its anti-inflammatory and immunosuppressive properties are the most used.

The complex action of GCs

GCs have both pro-and anti-inflammatory roles in specific conditions. Pro-and anti-inflammatory properties are necessary for the inflammation condition as a protection mechanism for return to normal tissue homeostasis. The anti-inflammatory chemicals annexin-1, SLP1, MOP-1, IB-, GILZ, and nitric oxide synthase were secreted to release GCs at low and high levels. However, GCs realized in high doses can decrease the production of pro-inflammatory compounds, including cytokines, chemokines, adhesion molecules, and pro-inflammatory enzymes, like phospholipase A2 and cyclooxygenase (120). Anti-inflammatory effects of GCs are principally mediated by trans-repression, while their side effects are principally mediated by gene expression activity. For example, a microarray-based study of murine T lymphoma cells has identified 44 direct GC targets (i.e., genes whose upregulation by GC was not prevented by cycloheximide) (121). Gene-activating and gene-suppressing by glucocorticoid receptors (GR) are its clinical benefits. These dissociation properties of GCs selectively mediate trans-repression more than transactivation (122,123).

Trans-repression is a dominant mechanism for inhibition of inflammation, but with a significant limitation; hence only when GCs exist through the period of active transcription can it be effective. GCs have long been known to inhibit inflammatory gene expression at a post-transcriptional level via destabilization of mRNA or inhibition of translation (124). In an experimental setting, GCs can block gene expression even if added after stimulation of the pro-inflammatory, whereas transcriptional inhibitors are

ineffectual (120).

GCs as anti-inflammatory mediators

In humans, GCs inhibit the transcription of pro-inflammatory cytokines produced by monocyte/macrophage cells such as IL-1β, IL-6, IL-12, TNFα, or GM-CSF, and down-regulate gene expression of chemokines, including IL-8, set RANTES and MCP-1 (125,126). GCs act on naive monocyte/macrophage cells and lead to anti-inflammatory mediators and differentiation of its phenotypes. These GC-induced anti-inflammatory monocytes with increased ability can migrate toward inflammatory stimuli. They can eliminate endogenous and exogenous risked signals via amplified phagocytic capacity, production of the anti-inflammatory mediators, and extent of T-cell activation. Thus, GCs inhibit the elevation of the inflammatory response in these cells by inhibiting the activation of pro-inflammatory macrophages and enhancing the anti-inflammatory activity in monocyte/macrophage populations, further eliminating inflammation (127). Physiologic actions of GCs are widespread, like glucose mobilization through amplified gluconeogenesis (hyperglycemia), subsequently augmented the insulin secretion and glycogen storage, and then redeployment of fat, protein disruption, and immunosuppression. This immunosuppression occurs from kinases inhibition responsible for cytokine production and from inhibition of the nuclear transcription factor NF-κB, an essential stimulator for the transcription of cytokines, chemokines, and additional molecules in the inflammation pathway. GCs, by activation of histone deacetylase2 (HDAC2) and through activating the transcription factors such as CREB, AP-1, and NF-κB, can active the chromatin and finally increases gene transcription. GCs can activate chromatin by HDAC2 and transcription factors such as CREB, AP-1, and NF-κB and can ultimately increase gene transcription (120).

GCs/NFκB-α (IκB-α) and gene transcription

In mammals, NF-κB contains five proteins that mainly exist in the cytosol by deactivating either homo/heterodimers: RelA (p65), RelB, c-Rel, p105, and p100. The p105 and p100, as unique proteins, are essential for post-translational processing by the proteasome to form the active subunits p50 and p52 (128). These isoforms have a joint Rel homology domain, which can bind with DNA and inhibitory proteins in the cytosol, which is termed Inhibitor of –κB (IκB) (129). Activation of NF-κB induces gene transcription of negative regulators IκBα, IRAK-M, and the regulatory NLRs NLRP12, NLRX1, and NLRC3. The negative regulators of NF-κB signaling have a more critical role in controlling inflammation because they are controlled by NF-κB activation and help as a feedback mechanism for retaining the immune system homeostasis (130).

NF-κB signaling and transcriptional/post-transcriptional

The NF-κB signaling cascade process is a vital element of disease pathology and can significantly affect the targeted therapeutic strategies. NF-κB is a prominent inducible transcription factor which finds in Drosophila humans, with a vital role in the host immune response. NF-κB signaling is a dominant regulator for gene transcription and has a highly effective strategy used by the cell for modulating essential and various biological processes in inflammatory conditions (128). Their review article focused on the negative regulation of NF-κB signaling and recognized over 200 proteins that involve targeting and reducing NF-κB signaling. This high level of regulation induces a widespread and critical biological function related to NF-κB signaling in the different cells and in specific time conditions. It highlights the significance and complication of this signaling cascade at the transcriptional/post-transcriptional and post-translational levels (130). The other link for modulating NF-κB signaling by targeting RNA strategy is a highly effective negative feedback mechanism. MicroRNAs act in this manner as a special class of RNA with a regulatory function. They can robustly regulate the strength and translation of mRNA transcripts encoding key ingredients in the signaling cascade of NF-κB (131). This signaling cascade is a pro-inflammatory cell pathway, with the hypothesis that its inhibition may be a therapeutic approach in COVID-19 (132). Signaling of the pro-inflammatory cell pathway destroys IκB proteins and releases NFκB, which then enters the nucleus to activate target genes (133). Severe inflammatory phenotypes in mice lacking IκB-α cause their death, newborns, immediately after birth (134). Therefore, the NF-κB signaling pathway as the center of a molecular mechanism for controlling inflammation can make the biochemical cascade for positive and negative regulatory pressure. However, negative regulators of NF-κB signaling play an essential role in controlling inflammation by the feedback mechanism to maintain immune homeostasis. However, any shift in this delicate balance can have significant and far-reaching biological effects. Moreover, an additional level of control arises from the crosstalk between these

two pathways. Indeed, some molecules can limit the activation of one pathway or trigger the other. Therefore, these complex negative regulators can be critical for better understanding the unique biological functions and physiologic responses, explaining clinical relations, and better therapeutic strategies for targeting the control of the anarchical inflammation. Stress is a vital response in maintaining the equilibrium of cells' internal environment for organisms against environmental changes. CRH and NA from the LC nucleus are the main factors in stress response, and inflammation indicates homeostasis abnormalities. GCs control the stress response through changing gene expression, transcription, and translation at the molecular level. Therefore, GCs present inhibitory actions on the transcription and function of different cytokines. GCs decrease the proliferation, variation, stimulation, and existence of T cells and macrophages. GC inhibits Th1 and macrophage-based inflammatory cytokines, including IL-1β, IL-2, IL-6, TNF-α, and IL-17135 (135).

Discussion

Two years has passed since the outbreak of COVID-19 in China and its global expansion, which unfortunately has a significant impact on public health and the global economy. The amount of scientific information collected on all aspects of this viral infection has so far failed to respond to organ involvement and disruption of the body's hemostatic processes in neuro-immune modulations. So, information is still needed to define new diagnostic, therapeutic, or prophylactic protocols. We have no reports of asymptomatic infected individuals, and immune studies indicate a T cell-dependent reaction in patients with moderate infection. However, in patients with severe symptoms and intensive systemic inflammation, signs of burnout are seen in T cells. Therefore, these fundamental aspects should be done in close cooperation with clinicians and basic researchers with the strong support of financial agencies, whether public or private. The main challenge now is how to use these studies and conceptual sciences for clinical benefit. We still do not know why people's immune responses to COVID-19 are different. This differentiation must link to the people's immune system. Therefore, the role of other systems in this interaction becomes severe and necessary. The nervous system controls the immune system, and the irregular immune response leads to a cytokine storm at the border of the innate and adaptive immune system, which may be accompanied by an unsuccessful defense response in hospitalized patients or a cytokine storm.

Therefore, we must have correct responses to under question:

1) How much fear and stress can affect the disease process of hospitalized patients or trigger the cytokine storm? CRH at the hypothalamic level controls adrenocorticotropic hormone (ACTH) release by the anterior pituitary and the cortisol secretion from the adrenal cortex by a negative feedback loop for the GCs production. CRH in the LC nucleus increases the tone of the adrenergic neuronal activation. This amplification causes the promotion of anxiety-like behavior. Can these interactions between the nervous, endocrine, and immune systems lead to psychiatric symptoms? Cortisol, the effective primary adrenal hormone, was significantly raised through activation in the chronic fatigue syndrome (CFS) in virus infection. This activation is related to the abnormal HPA negative feedback regulation or excessive stimulation (136). The serum level of cortisol during CFS at a steady state is low, and often an experience of physical or emotional stress through activation of the HPA axis leads to more release of cortisol and ACTH. ACTH/GCs amplify catecholamine secretion, and therefore, pathologic signs of these positive feedback systems can be hypoxia, hypoglycemia, hypercapnia acidosis, hemorrhage, and increasing the sympathetic nervous system (SNS) stimulation.
2) How can this positive feedback system (neuroendocrine) be broken? The SNS is the first line against viral infection activated by the changes in the body's internal homeostasis with the emergency response (fight and flight). SNS is a part of persistent regulatory machinery for hemostasis stability. Of course, the SNS is not an alone system in acting on this task. The local activation of immune cells by antigen enters leads to the release of pro-inflammatory mediators, and this local signal is robust enough for sending signals via circulation to the brain and activation of the HPA axis. Pro-inflammatory cytokines (IL-1, IL-6, and TNF) are produced by local activation of the innate immune cells and are essential for this linkage from the immune system to the central nervous system (CNS). Dysregulation of the innate/adaptive immune systems increases the inflammatory response via the autonomic nervous system (ANS) and causes induction of the onset or acceleration of pathological

processes (cytokine storm).

3) How can resistance against cytokine storm?

   The sympathetic tone was associated with IL-6 plasma levels, and stress responses excessively influence inflammation. However, massive levels of cytokines can cause extensive lung damage and acute respiratory distress syndrome. The intolerable cytokine storm can be a significant cause of organ damage even beyond the lungs and its extension to the kidneys and heart and death.

4) Is anti-cytokine therapy a correct solution? Was Tocilizumab a successful drug as an antagonist of the interleukin-6 receptor in hospitalized patients with coronavirus disease? Cytokine blockers have tolerable safety characteristics despite their rapid rate of action and high response rate. However, anti-cytokine therapy can reason for an increase in infections or reactivation.

The relationship between virus/host can probably impair connections between the neuroendocrine and immune systems and can lead to psychiatric symptoms with the activation of the Psycho-neuroendocrine-immune system, which causes complex reactions and confusion of defense processes. There is much evidence connected between augmented levels of pro-inflammatory cytokines and depression disorder. The chronic inflammatory condition is described by overactivity of the SNS/HPA but without immunosuppression (GC-R desensitization and insufficiency) and local excretion of SNS fibers from inflamed tissue, including lymphatic organs, allows inflammatory margins to form (plasticity process). An inflammatory disease with chronic activation of the HPA axis causes significant depression and probably metabolic syndrome, which can be increased cardiovascular risk from undesirable exogenous GCs effect. It should be noted that GC resistance can be a finding for the neurophysiological changes against augmented stress response.

The centrally controlled by SNS can able increas the primary response to the inflammation. Therefore, the interaction with immune cells at local and central sites of inflammation shows a net anti-inflammatory effect.

Is it possible that the administration of a central adrenergic system antagonist before the onset of the cytokine storm can prevent the onset of this storm from a prophylactic role?

At the beginning of the inflammatory process, the body needs to amplify the systemic activity of the SNS and HPA axis for the metabolic processes of enough energy-rich fuels, to perform the needs of an activated immune system.

In chronic inflammation, there is still SNS/HPA hyperactivity without immunosuppression of GC and local repulsion of SNS fibers from lymphoid organs to produce progressive zones of permitted inflammation. NA has a greater affinity for binding to alpha receptors than beta-adrenoceptors, and simultaneous expression occurs at the surface of immune cells. Therefore, pattern of the adrenoceptors' expression, cytokine milieu, and catecholamine source distance is vital for immune response. Firstly the SNS signals are pro-inflammatory, while anti-inflammatory properties are principal at the latency or chronic phase of the inflammatory response. SNS activity at the local site of inflammation is mostly the direct result of the neurotransmitter effect on the immune cells (137). Alpha-2 adrenoceptors also activate macrophages to detect an anti-inflammatory response (138), and agonists of α2adrenoceptors reduce TNF production (139). The immune response is coupled with central regulation for the anti-inflammatory effect of the brain. Therefore, the final output of SNS activity during the inflammatory process can be explained by the adrenoceptors' expression pattern on the immune cells. The net effect of Clonidine is a reduction of sympathetic tone. Our choice for Clonidine mainly was based on its central mechanisms, which include: 1) reduction of the sympathetic nervous system tone by the activity of pre-synaptic adrenergic α2 (autoreceptor), 2) prescribing it to treat psychiatric disorders, and 3) the stimulation through α-adrenoceptors has a pro-inflammatory effect. Clonidine via epidural, intrathecal, and local/topical routes can be effective in chronic pain (140), the pain after children's operation (141), and neuropathic pain (142). Dose dependently on Clonidine can suppress plasma levels of NA (143), blood pressure and cardiac output (144), lowered body temperature (145), and it has sedative effects (146) in healthy subjects. All of Clonidine's properties were taken into account in this study. Because of its ability to maintain hemodynamic stability, Clonidine can be a helpful drug in intensive care. Our studies on clonidine in women with polycystic ovaries have shown that its sedative role can reduce stress in patients and has played an effective role in animal studies and in culture media (26, 147,148,149). Clonidine is an appropriate candidate for pharmacotherapy when patients with COVID-19 infection are admitted to the hospital in the psycho-neuroendocrine-immune aspect. Stress and fear of hospitalization in COVID-19 patients can activate the sympathetic nervous system and the HPA axis, which in turn activates the immune system and the inevitable

psychological processes in these patients that affect the patient's physical and mental condition.

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