Review Article

Dexamethasone, interleukin 6, LTB4, and the endocrine gland are the real battles for COVID-19: our molecular docking, physiological, and immunological explanations

Abstract:

Nearly two years after the lethal pandemic of COVID-19, which is considered a joker virus that may bypass many immune defenses in our bodies, such as innate and adaptive immunity, with all types of cells, there are important markers at the long road for treatment, such as interleukin (Il-6), neutrophils, high ferritin, and high D dimer. Additionally, post-COVID-19 or long COVID-19 effects include neuropsychiatric problems such as smell dysfunctions and hormonal dysfunctions. Therefore, this article will highlight the adrenal gland as a place where the immune and endocrine systems meet. Additionally, dexamethasone does not affect Il-6 secreted from the adrenal cortex, which allows Il-6 to be produced during stress. We need a new classification of IL-6 at physiological and pathological aspects, as the stimulatory factors are different. Endocrine Il-6 is stimulated by ACTH, but immune Il-6 is stimulated by il-1β and angiotensin II. Of note, dexamethasone critically saves COVID-19 patients but has no effect on Il-6 of endocrine (ACTH stimulated) origin, either basal or stimulated. Therefore, the adrenal gland serves as a vital link between the endocrine and immunological systems in the pathogenesis of COVID-19. In addition, Il-6 is the key sex-linked variation in immune responses. Some conditions are known to stimulate the hypothalamic-pituitary-adrenal axis, such as mycobacteria, viral infections, strenuous exercise, or academic stress, which may affect leukocyte glucocorticoid sensitivity, which decreases. LTB4 may have a role in respiratory failure and water in the lung, as it is a milestone at the metabolite of arachidonic acid and plays a role in the HPA axis, so more clinical studies are needed about its role in HPA axis stimulation. We studied the molecular docking of dexamethasone with

interleukin-6 and showed the binding interaction of dexamethasone with interleukin-6. It shows binding affinity was found -6.7 Kcal/mol

Keywords: dexamethasone, ACTH, endocrine, interleukin 6, LBT4, covid-19, cortisol, adrenal gland, resistive breathing

Introduction

It is well recognized that hypothalamic corticotropin-releasing hormone (CRH) is responsible for pituitary activation and the synthesis of adrenocorticotropic hormone (ACTH), which provokes the adrenal cortex to generate glucocorticoids (GCs).

Interleukin-6 (IL-6) is generated by adrenal gland zona glomerulosa cells and is controlled by IL-1α, IL-1β, ACTH, and angiotensin II. The synthetic glucocorticoid dexamethasone is particularly effective toward immune organs such as the spleen and all immunological tissues. Dexamethasone is regarded as an IL-6 inhibitor in various tissues. However, it showed no effect on IL-6 production in the adrenal gland. ACTH is a conventional endocrine hormone, and the combined effect of IL-1β and ACTH can release much more IL-6 than the individual effect of each one alone [1].

Of note, IL-6 generated by cells of zona glomerulosa could be passed to the zona reticularis and zona fasciculata through adrenal blood supplies that connect these regions. The physiological responses of the hypothalamic-pituitary-adrenal (HTPA) axis might also be influenced by adrenal IL-6. Previous studies demonstrated that IL-1 and IL-6 stimulated ACTH production and release and that ACTH triggered IL-6 generation in rat zona glomerulosa cells. ACTH and angiotensin II did not influence IL-6 generated by zona fasciculata or reticularis [1, 2].

In both animal models and humans, estrogens improve humoral immunity while decreasing cellular responses, whereas androgens inhibit mechanisms. In addition, females are more usually seriously impacted by autoimmune diseases. The same study found that males produced considerably more ACTH than females. Additionally, intravenous infusions of ACTH and cortisol stimulate IL-6 secretion in healthy young people [3]. Interestingly, both at the start of the study and after IL-6 stimulation, females had considerably greater cortisol/ACTH ratios than men. These findings imply that the generation of GCs in males and females requires comparable amounts of IL-6. They do, however, show that male and female adrenals have distinct

sensitivity to ACTH and perhaps to direct IL-6 activation. Overall, in males but not in females, peak cortisol values were substantially connected to circulating IL-6 levels, but the relationship between ACTH and cortisol levels was inverted. In addition, females had significantly higher cortisol/ACTH ratios than males, suggesting that high estradiol levels after menopause or postmenopause keep cortisol levels high in relation to plasma levels of ACTH [3]. In addition, testosterone reduces the rat HTPA axis response to IL-6. This suggests that in the presence of gonadal steroids, several processes, parallel to the regulation of IL-6 production, are involved in limiting the HTPA inflammatory response [4]. In severe COVID-19 patients, dexamethasone altered neutrophils, changed IFN^{active} neutrophils, suppressed interferon-stimulated genes, and activated IL-1R2+ve neutrophils. Dexamethasone also increased the number of immunosuppressive immature neutrophils and changed cellular connections by switching neutrophils from information receivers to producers.

Male COVID-19 patients exhibited a larger proportion of IFN^{active} neutrophils than female patients and favored steroid-induced immature neutrophil development, which might affect outcomes. "Specifically, in men, we detect an increased neutrophil interferon response that is greatly inhibited when a patient is given dexamethasone," Biernaskie said. Females, on the other hand, "had a considerably more tempered neutrophil interferon response, therefore dexamethasone had less impact." Dexamethasone showed different effects according to sex, which could have serious consequences for sex-dependent findings and treatment impact in serious COVID-19 symptoms [5].

Nuclear factor-kappa B (NF-kB) is the principal modulator of IL-6, and the first study established steroid suppression of NF-kB in the cells of early newborns with breathing difficulties by Aghai et al. This study further demonstrates that dexamethasone's anti-inflammatory impact in preterm newborns may be mediated by NF-kB, which is important for controlling the key inflammatory mediators linked to acute lung damage. Steroids' anti-inflammatory impact via suppression of pro-inflammatory cytokines might be achieved by suppression of the transcription factor NF-B [6]. Human respiratory smooth muscle IL-6 production triggered by bradykinin via B2 receptors is responsive to corticosteroids and controlled by cytokines secreted by T helper cells.

Dexamethasone inhibited NF-kB-induced IL-6 production nearly entirely, lowering it by more than 95%. Because dexamethasone was somewhat successful at reducing IL-6 production as a reflex to TNF-α, the suppressing impact of dexamethasone on IL-6 transcription appears to be sensory, implying that cytokine receptors and GPCRs may control IL-6 gene expression via separate subsequent mechanisms. In airway smooth muscle (ASM) cells, dexamethasone fully inhibited BK-induced IL-8 expression. Dexamethasone reduces the capacity of BK to create prostaglandin E2 (PGE2), a crucial route in the control of IL-6 production in ASM cells, which may reduce IL-6 expression. The anti-inflammatory effects of dexamethasone and steroids are mediated in part by interactions with transcriptional regulators, such as activator protein 1 (AP-1) and NF-kB [7]. Research published in the journal Nature found that dexamethasone halted nearly a third of deaths in severe COVID-19 patients. Steroids, however, showed little impact on patients with moderate instances of COVID-19. Researchers hypothesize that the anti-inflammatory response of dexamethasone may be connected to its therapeutic impact on severely sick COVID-19 patients. However, the vast majority of serious cases suffer from crucial illness-related corticosteroid insufficiency (CIRCI), and dexamethasone's therapeutic potential might be due to its increase in the cortical role [8].

Table 1: Types of interleukins 6 according to the stimulatory effect:

Immune IL-6	**Endocrine IL-6**	**Type I adrenal steroid receptors**	**Type II adrenal steroid receptors**
IL-1α, IL-1β angiotensin II	ACTH stimulated	Mineralocorticoid receptors	Glucocorticoid receptors
Dexamethasone effect	No dexamethasone effect	High affinity for endogenous cortisol	High affinity to synthetic glucocorticoids dexamethasone
Zona glomerulosa	Zona glomerulosa	Aldosterone agonists significantly decrease levels of plasma neutrophils and	Significant increase in neutrophils and natural killer cells after application of type ii

		natural killer (NK) cells	receptors agonists RU28362

Since dexamethasone is not tied to corticosterone-binding globulin (CBG), it can reach all immune systems equally, relinquishing the exact properties provided by endogenous hormones. Adrenaline hormones can affect both cellular proliferation and maturation within the bone marrow, particularly T cells within the thymus. Adrenaline hormones have been proven to alter the ratio of macrophages to granulocyte progenitors by reducing macrophage colony formation by 75% to 90% while increasing granulocyte colony formation by 50% to 100%. Cortisol has also been shown to prevent PMA-induced monocyte-to-macrophage development in the monocytic cell line U-937 in humans. The potential of adrenal hormones to promote programmed cell death, also known as apoptosis, is one of the most dramatic elements of their effect on immune cells. Treatment with glucocorticoids lowered the blood levels of eosinophils and basophils, which is assumed to be connected to cell redistribution from the blood to the spleen and other compartments. Surprisingly, glucocorticoids boost neutrophil counts while reducing while simultaneously decreasing the number of circulating immune cells [9]. Adrenaline hormones are hypothesized to promote blood neutrophil levels by increasing neutrophil exit from bone marrow, delaying neutrophil outflow from circulation, and lengthening the half-life of circulating neutrophils. After one session of confinement, minor yet severe stress, macrocytopenia, and leukopenia, as well as macroneutropenia, were observed in the peripheral blood of rats [9].

It has been discovered that diurnal fluctuations in circulating lymphocytes occur in healthy people but not in individuals with adrenal insufficiency. These data also imply that cortisol administration decreases lymphocytic counts in a dose-dependent manner. In addition, prior research found that adrenalectomy eliminates diurnal regularity in lymphocyte counts and that a single dosage of prednisolone caused a reverse drop in lymphocytic counts immediately after medication delivery. Aside from their effect on normal leukocyte dispersion [9].

GCs prevent neutrophil, eosinophil, and monocyte-macrophage entry into inflammatory areas in the absence of infection or inflammation. This is regarded as a significant way to reduce inflammation caused by glucocorticoids. Adrenal hormones

have been shown to alter cytokine receptor expression and cytokine production. The synthesis of the IL-2 receptor a and b chains has been demonstrated to be suppressed by GCs at both the transcriptional and posttranscriptional stages. The fact that glucocorticoids inhibit IL-2-driven lymphocyte proliferation adds to this [9]

It has been shown that glucocorticoids increase the amount of IL-1 and IL-6 receptors. Another kind of acute immunopathology may emerge as a result of increased cytokine production during infections. This route was revealed in gram-negative bacterial sepsis septic shock. Lipopolysaccharide (LPS), a bacterial endotoxin, activates mononuclear phagocytes under these circumstances, resulting in extremely high cytokine production.

TNF-α, IL-1, and IL-6 cytokine cascades are activated. TNF-α production promotes the production of IL-1 and IL-6. IL-12 and interferon-g (IFN-g) are expressed too early in the cytokine storm [9].

Septic shock syndrome is a life-threatening condition marked by circulatory collapse and leakage, in addition to intravascular coagulation. Interactions between T cells can lead to the generation of harmful cytokines. Bacterial superantigens induce abnormally high levels of T lymphocytes in naive hosts, possibly contributing to the septicemia linked with some infections caused by gram^{+ve} bacteria. Additionally, higher cytokines produced by T helpers have been associated with the pathology of hemorrhagic disease caused by dengue virus (Dengue fever) and recurrent dengue virus infection lung immunopathology. These are some of the scenarios in which an "overactive" immune response might cause illness [9].

Glucocorticoids are potent regulators of the immune response. The arrangement of adrenal steroid receptors differs between kinds of immune cells, as do the effects of adrenal steroids on the immune modulator reflex or synthesis. Adrenal steroids function to defend the body by blocking overshooting immune responses. During infection, the hypothesis is that elevations in adrenal steroids help immune system cells hurry their fight regions at the time of infection or metastasis of cancer cells [10, 11].

As B lymphocytes, lacking from the lung beneath regular conditions, and B cells are the maximum delicate lymphocytes for glucocorticoids, and glucocorticoids impact

the dissemination of lymphocytes withinside the body, it is far possible that B lymphocytes are probably defenseless toward stress-instigated heights of glucocorticoids. [12].

Dexamethasone is not tied to corticosteroid proscribing globulin (CBG) and thus has equal admittance to each unmarried invulnerable compartment. New statistics suggest that interleukin-12 (IL-12) and IFN-γ – (kind II interferon) are probably communicated extraordinarily earlier than withinside the cytokine course [13], accordingly for the duration of viral contaminations, pinnacle IL-12 and (IFN-γ) came about for the duration of the middle degree with the shift to IL-four at past due degree, endogenous glucocorticoids may improve this shift and can expect a component at IFN initiated rearrangement of lymphocytes from dissemination to neighborhood lymph hubs and splenic white mash regions and one extra activity of glucocorticoids is probably extensive for the duration of starting degree is a reallocation of mononuclear cells from fringe blood to lymphoid compartments [14–17]. In viral infections, acute immunopathology can result from excess production of cytokines. Utilizing portions of trial murine viral fashions for concentrating at the enlistment and potential of steroids as intranasal contaminations with flu contamination observe good-sized lung pathology and the insusceptible response arises to feature to something like a volume of this harm [18–22] as against intraperitoneal sicknesses with LCMV [23, 24] which display decrease negligible pathology so extra damage befell with an intranasal version so fashions supply tremendous statistics approximately diverse pathways of steroid popularity all through infections.

The accessibility of coursing corticosteroids organically to adrenal receptors in exclusive invulnerable tissues is directed with the aid of using corticosteroid proscribing globulin (CGB) and liver - inferred plasma protein and it is far giant spotlight intensifies that dexamethasone and several engineered corticosteroids are not restrained with the aid of using CBG so why electricity of those synthetic steroids in vivo comparative with cortisol or corticosterone so beneath Neath standard situations over 90% of flowing corticosteroid is sure to CBG so the extent and appropriation of CBG is the important thing in guiding principle of prescribing of endogenous chemical substances to adrenal steroid receptors that is the cause the dexamethasone is quite extreme in obtaining access to insusceptible booths like spleen [25].

Pregnancy is a variable that adjusts the CBG level, as estrogen upregulates CBG creation, which serves to generally balance the raised cortisol creation present at present.

As of the hour of the day on adrenal receptor enactment, increased admittance of glucocorticoids to secure compartment recognized with dull as Diurnal modifications withinside the dispersion of fringe blood insusceptible cells which same adjustments in coursing tiers of corticosterone are likewise constant with the increased admittance of glucocorticoids to this secure compartment [26].

Generally, the assessed adrenal steroid receptor actuation became extra distinguished in thoughts than in pituitary or invulnerable tissue, and internal a selected tissue, there has been an extra noteworthy stage of assessed enactment of the adrenal steroid excessive fondness kind I receptor than of the type II receptor. There became an extra noteworthy actuation of thought kind II receptors via basal corticosterone to withinside the PM (30-35%) compared with the AM (5-15%). As excessive stress added comparative stages of receptor enactment on the two times of day (45-half), the internet alternate in kind II receptor initiation withinside the thoughts later excessive stress became plenty extra modest withinside the PM than withinside the AM. This suggests that there are probably diurnal contrasts within the task of kind II receptors in corticosterone-bad complaints at the hypothalamic-pituitary-adrenal pivot. In susceptible tissues, kind II receptor enactment via means of excessive stress became especially heterogeneous, contingent upon each the resistant category and the hour of the day, recommending that those are significant factors including a difference in the influence of corticosterone on invulnerable reactions in the course of excessive stress. Taken together, our effects propose that the phasic and tonic actions of corticosterone on the course tissue reactions no longer simply with the diurnal and strain emission examples of corticosterone but moreover with target tissue factors, such as type I and sort II receptor articulation and chemical bioavailability. These elements are uploaded to massive precision of response for the foundational chemical corticosterone [27].

The conditions that are known to stimulate the hypothalamic-pituitary-adrenal axis, such as mycobacteria, viral infections, strenuous exercise, or academic stress, may affect leucocyte glucocorticoid sensitivity, which decreases. This explains why dexamethasone has no effect on interleukin-6 stimulated by ACTH during HPA axis

stimulation during viral infections, and the inhibitory effect of dexamethasone on both IL-6 and TNF-α secretion was significantly reduced following exercise because this exercise was accompanied by HPA axis activation and increased ACTH, which stimulated IL-6 secretion immediately after exercise. Resistance to dexamethasone may occur, as there are interindividual differences in GC responsiveness. Additionally, intraindividual differences have been reported, suggesting dynamic regulation of GC sensitivity, so such decreased responsiveness could have therapeutic consequences when occurring in inflammatory disorders (28)

Therefore, activation of HPA by cytokines through the release of glucocorticoids has been found to play a critical role in restraining and shaping immune responses. Thus, cytokine-HPA interactions represent a fundamental consideration regarding the maintenance of homeostasis and the development of disease during viral infection. (29)

Leukotriene B4 is considered a milestone metabolite of arachidonic acid and may have a role in the pathophysiology of acute respiratory failure. As in a study by Olson NB et al., endotoxin increased the levels of LTB4 and albumin in bronchoalveolar lavage fluid (BALF). In a porcine endotoxemia model, DEX blocked or greatly attenuated the endotoxin-induced increases in plasma and LTB4 levels. (30) Another study in pigs also studied the effect of NSAIDs or dexamethasone on porcine pulmonary response to endotoxemia before and after administration of nonsteroidal anti-inflammatory drugs (NSAIDs, i.e., indomethacin or flunixin meglumine) or dexamethasone (DEX). Both NSAIDs and DEX blocked the endotoxin-induced increases in lung water, bronchoalveolar lavage (BAL) neutrophils, and BAL albumin content. The drop in plasma proteins persisted in NSAID but not DEX-treated pigs. The study concluded that endotoxemia in pigs causes severe acute respiratory failure largely mediated by cyclooxygenase and possibly lipoxygenase products of arachidonic acid metabolism. (31). Leukotrienes have been shown to regulate the hypothalamic-pituitary-adrenal (HPA) axis in a study by Hirai A for the involvement of 5 lipoxygenase metabolites in ACTH stimulated corticosteroid synthesis in the adrenal gland of a mouse model where metabolites of arachidonic acid have many potent biological activities and modulate physiological processes in many cells like endocrine cells and need more clinical studies are needed. (32)

Role of inhaled dexamethasone on il-6 stimulated by resistive breathing:

(Resistive breathing, interleukin-6, pulmonary edema, dexamethasone is interlocked:

Resistive breathing is breathing against increased airway resistance and issimilar to exercise for respiratory muscles and is linked with high negative intrathoracic pressures, increased mechanical stress promoting high permeability and pulmonary edema, and inflamed lungs. Inspiratory resistive breathing or strenuous contractions of the respiratory muscles occurred at many chronic respiratory diseases like COPD, asthma especially during attacks increases the plasma levels of proinflammatory cytokines like tumor necrosis factor (TNF-α). Interleukin 1β (IL-1β) and interleukin il-6, and stimulate the HPA axis which results in β-endorphin that affect breathing brain functions including sleeping and sensation of fatigue, also if resistive breathing continued can injure the respiratory muscles and acute lung injury, the study by Dimitris et al; give the possibility that the increased permeability of the alveolar-capillary membrane and pulmonary edema formation was noted earlier than inflammation after resistive breathing,(33) the pathophysiology of this mechanism is similar to what's happening of pulmonary edema at severe covid-19 cases where a study by Xinyu Cui et al; review the mechanisms which induce pulmonary edema and lead to severe critical cases of covid-19 patients and fluid accumulation in the alveolar airspace which cause mortality (34)

preliminary results from the study by Vassilakopoulos T et al; suggest that inspiratory resistive breathing leads to an increase of IL-6 in the induced sputum of healthy volunteers (35)

the origin of resistive breathing -stimulated plasma cytokines what's the origin?

data obtained by the study speculated that the origin of resistive breathing-induced plasma cytokines is not from monocytes but respiratory muscles so resistive breathing as a form of exercise restricted to respiratory muscles and antioxidants supplementation dramatically blunt the il-6 response and (TNF-α). and 1β (IL-1β) were undetectable (35)

the results of 2 studies show the beneficial effect of short term inhaled dexamethasone or intravenous on improving pulmonary functions, decreasing the respiratory resistance, and decreasing the inflammation for preterm infants at risk of bronchopulmonary dysplasia on the resistive airflow properties studied by M Pappagallo et al; and intravenous dexamethasone by Yoder MC et al; (36-37)

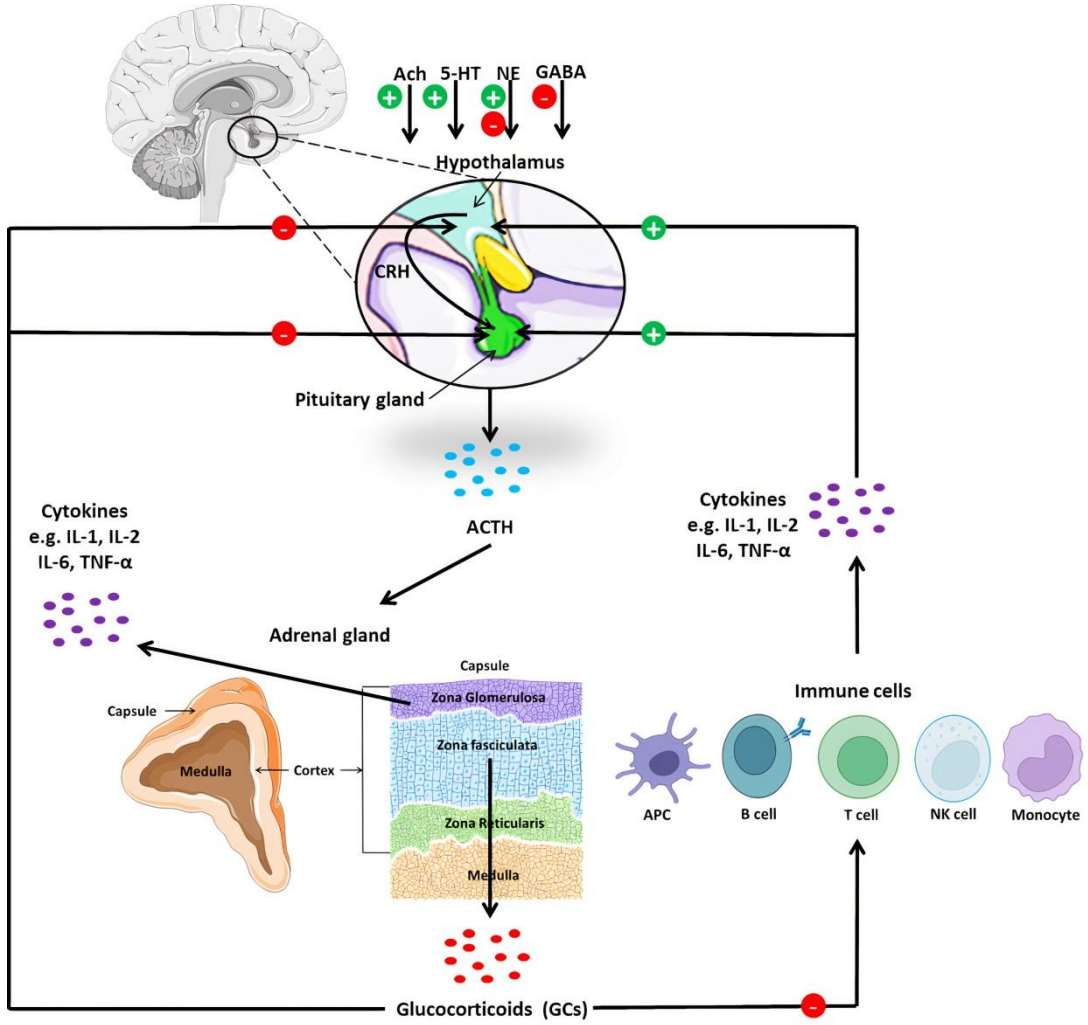

Figure 1. Schematic illustration of the hypothalamic-pituitary-adrenal axis (HTPA axis) and the immunomodulation pathway. Corticotropin-releasing hormone (CRH) from the hypothalamus is responsible for pituitary activation and releasing of adrenocorticotropic hormone (ACTH) which stimulates the adrenal cortex to secrete glucocorticoids (GCs). GCs (or dexamethasone as a synthetic example) have a critical role in immune suppression by blocking the secretion of proinflammatory cytokines (especially IL-6 released from endocrine origin or stimulated by ACTH) secreted by immune cells. On the other hand, dexamethasone suppresses the production of IL-6 in many different tissues, however, it has no impact on IL-6 produced in the adrenal cortex [1]. NE, Norepinephrine; GABA, gamma-Aminobutyric acid; 5-HT, 5-hydroxytryptamine; Ach, Acetylcholine; IL, Interleukins; TNF-α, Tumor necrosis factor.

In silico molecular docking of dexamethasone with IL-6

Using AutoDock Vina, the molecule dexamethasone was docked with the receptor interleukin-6 and analyzed for binding energy and protein-ligand interactions. The binding affinity was found at -6.7 Kcal/mol. PyMOL was used to create complex receptor and ligand files, while Discovery Studio was used to find interactions.

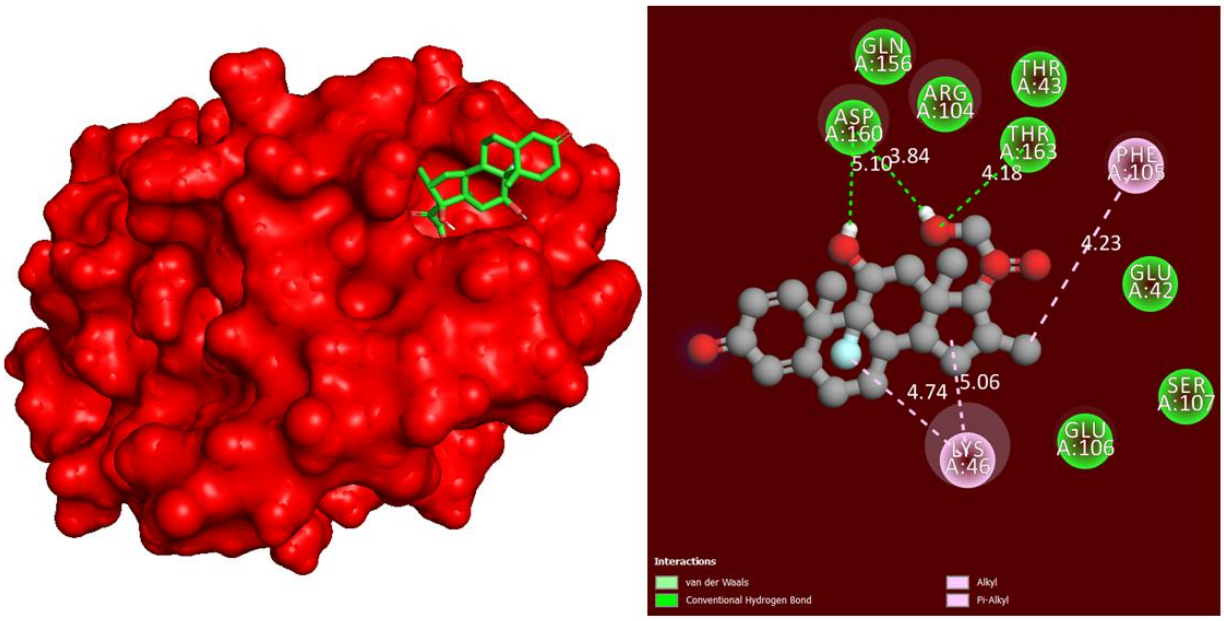

Figure 2 Binding interaction of dexamethasone with interleukin-6. It shows the binding pocket of protein in 3D and 2D. Important binding residues making different kinds of interactions present in the binding site are shown in the 2D image.

Abbreviations:

NSAIDs**:** Nonsteroidal anti-inflammatory drugs

DEX	Dexamethasone
ACTH	adrenocorticotropic hormone
AP-1	activator protein 1
ASM	airway smooth muscle
CBG	corticosterone binding globulin
CIRCI	critical illness-related corticosteroid insufficiency
CRH	corticotropin-releasing hormone
GCs	glucocorticoids
HPA	Hypothalamic-pituitary–adrenal
HTPA	Hypothalamic-pituitary–adrenal
IFN-g	interferon-g
IL	Interleukin
LPS	lipopolysaccharide
PGE2	prostaglandin E2
COPD	chronic obstructive pulmonary disease

Conclusions: In excessive cases, COVID-19 is a multisystemic indicator of infection with a cytokine typhoon signal. Dexamethasone is a joker drug and exquisite weapon in opposition to cytokine typhoon in coronavirus illness, as dexamethasone is incredibly sturdy toward the insusceptible framework with the aid of using its inability to tie to CBG and gaining access to each resistant compartment. Therefore, all secure tissues displayed equal and vast type II receptor enactment depending upon the fact that dexamethasone went in opposition to endogenous glucocorticoids since it is not impacted while of day ether dim or dynamic period. Adrenal receptor enactments infringe blood lymphocytes with the aid of stress-induced heights in corticosterone take place at dim periods. With the aid of atomic docking, dexamethasone was combined with interleukin-6. It indicates limiting liking turned into found - 6.7 Kcal/mol. Be that because it may, dexamethasone does not affect ACTH-stimulated Il-6 discharged from the adrenal cortex. LTB4 may have a role in respiratory failure and water in the lung, as it is a milestone at the metabolite of arachidonic acid and plays a role in the HPA axis, so more clinical studies are needed about its role in HPA axis stimulation. Resistive breathing produces cytokines like strenuous exercise which also induces a plasma cytokine response. Resistive breathing may be the hallmark at the critical stage of covid-19 and progressing to pulmonary edema.

COMPETING INTERESTS DISCLAIMER:

Authors have declared that no competing interests exist. The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

References:

1. Judd AM, MacLeod RM (1992) Adrenocorticotropin increases interleukin-6 release from rat adrenal zona glomerulosa cells. Endocrinology 130:1245–

1254. https://doi.org/10.1210/endo.130.3.1311232

2. Jones TH (1994) Interleukin-6 an endocrine cytokine. Clin Endocrinol (Oxf) 40:703–713. https://doi.org/10.1111/j.1365-2265.1994.tb02502.x

3. Silva C, Ines LS, Nour D, et al (2002) Differential male and female adrenal cortical steroid hormone and cortisol responses to interleukin-6 in humans. Ann N Y Acad Sci 966:68–72. https://doi.org/10.1111/j.1749-6632.2002.tb04203.x

4. Papadopoulos AD, Wardlaw SL (2000) Testosterone suppresses the response of the hypothalamic-pituitary-adrenal axis to interleukin-6. Neuroimmunomodulation 8:39–44. https://doi.org/10.1159/000026451

5. Sinha S, Rosin NL, Arora R, et al (2021) Dexamethasone modulates immature neutrophils and interferon programming in severe COVID-19. Nat Med. https://doi.org/10.1038/s41591-021-01576-3

6. Aghai ZH, Kumar S, Farhath S, et al (2006) Dexamethasone suppresses expression of Nuclear Factor-kappaB in the cells of tracheobronchial lavage fluid in premature neonates with respiratory distress. Pediatr Res 59:811–815. https://doi.org/10.1203/01.pdr.0000219120.92049.b3

7. Huang C-D, Tliba O, Panettieri RAJ, Amrani Y (2003) Bradykinin induces interleukin-6 production in human airway smooth muscle cells: modulation by Th2 cytokines and dexamethasone. Am J Respir Cell Mol Biol 28:330–338. https://doi.org/10.1165/rcmb.2002-0040OC

8. Mao Y, Xu B, Guan W, et al (2020) The Adrenal Cortex, an Underestimated Site of SARS-CoV-2 Infection. Front Endocrinol (Lausanne) 11:593179. https://doi.org/10.3389/fendo.2020.593179

9. McEwen BS, Biron CA, Brunson KW, et al (1997) The role of adrenocorticoids as modulators of immune function in health and disease: neural, endocrine and immune interactions. Brain Res Brain Res Rev 23:79–133. https://doi.org/10.1016/s0165-0173(96)00012-4

10. Munck, A. and Guyre PM (1991) Glucocorticoids and immune function. R Ader, DL Felten N Cohen _Eds., Psychoneuroimmunology, Acad Press San Diego, 447–474.

11. Munck A, Guyre PM, Holbrook NJ (1984) Physiological functions of glucocorticoids in stress and their relation to pharmacological actions. Endocr Rev 5:25–44. https://doi.org/10.1210/edrv-5-1-25

12. McGregor BA, Murphy KM, Albano DL, Ceballos RM (2016) Stress, cortisol, and B lymphocytes: a novel approach to understanding academic stress and immune function. Stress 19:185–191. https://doi.org/10.3109/10253890.2015.1127913

13. Tjan LH, Furukawa K, Nagano T, et al (2021) Early Differences in Cytokine Production by Severity of Coronavirus Disease 2019. J Infect Dis 223:1145–1149. https://doi.org/10.1093/infdis/jiab005

14. Gresser I, Guy-Grand D, Maury C, Maunoury MT (1981) Interferon induces

peripheral lymphadenopathy in mice. J Immunol 127:1569–1575

15. Ishikawa R, Biron CA (1993) IFN induction and associated changes in splenic leukocyte distribution. J Immunol 150:3713–3727

16. Korngold R, Blank KJ, Murasko DM (1983) Effect of interferon on thoracic duct lymphocyte output: induction with either poly I: poly C or vaccinia virus. J Immunol 130:2236–2240

17. Woodruff JF, Woodruff JJ (1970) Virus-induced alterations of lymphoid tissues. I. Modification of the recirculating pool of small lymphocytes by Newcastle disease virus. Cell Immunol 1:333–354. https://doi.org/10.1016/0008-8749(70)90053-5

18. Dunn AJ, Powell ML, Meitin C, Small PAJ (1989) Virus infection as a stressor: influenza virus elevates plasma concentrations of corticosterone, and brain concentrations of MHPG and tryptophan. Physiol Behav 45:591–594. https://doi.org/10.1016/0031-9384(89)90078-4

19. Feng N, Pagniano R, Tovar CA, et al (1991) The effect of restraint stress on the kinetics, magnitude, and isotype of the humoral immune response to influenza virus infection. Brain Behav Immun 5:370–382. https://doi.org/10.1016/0889-1591(91)90032-6

20. Hermann G, Tovar CA, Beck FM, et al (1993) Restraint stress differentially affects the pathogenesis of an experimental influenza viral infection in three inbred strains of mice. J Neuroimmunol 47:83–94. https://doi.org/10.1016/0165-5728(93)90287-9

21. Hermann G, Tovar CA, Beck FM, Sheridan JF (1994) Kinetics of glucocorticoid response to restraint stress and/or experimental influenza viral infection in two inbred strains of mice. J Neuroimmunol 49:25–33. https://doi.org/10.1016/0165-5728(94)90177-5

22. Sheridan JF, Feng NG, Bonneau RH, et al (1991) Restraint stress differentially affects anti-viral cellular and humoral immune responses in mice. J Neuroimmunol 31:245–255. https://doi.org/10.1016/0165-5728(91)90046-a

23. Biron, C.A., Miller, A.H., Spencer, R.L., Leung, J.J., Theroux, D.N., Orange, J.S., Salazar-Mather, T., Su, H.C., and McEwen BS (1994) Adrenal steroid-mediated regulation of immune responses to LCMV infection. FASEB J 8:976

24. Miller, A.H., Biron, C.A., Spencer, R.L., Tanapat, P., Leung, J., Dhabhar, F., and McEwen BS (1994) Effects of viral infections on adrenal steroid secretion and adrenal steroid receptor expression. Soc Neurosci 7:952

25. Miller AH, Spencer RL, Trestman RL, et al (1991) Adrenal steroid receptor activation in vivo and immune function. Am J Physiol 261:E126-31. https://doi.org/10.1152/ajpendo.1991.261.1.E126

26. Sabbioni ME (1993) Psychoneuroimmunological issues in psycho-oncology. Cancer Invest 11:440–450. https://doi.org/10.3109/07357909309018875

27. Spencer RL, Miller AH, Moday H, et al (1993) Diurnal differences in basal and

acute stress levels of type I and type II adrenal steroid receptor activation in neural and immune tissues. Endocrinology 133:1941–1950. https://doi.org/10.1210/endo.133.5.8404640

28- Smits HH, Grünberg K, Derijk RH, Sterk PJ, Hiemstra PS. Cytokine release and its modulation by dexamethasone in whole blood following exercise. Clin Exp Immunol. 1998;111(2):463-468. doi:10.1046/j.1365-2249.1998.00482.x

29- Silverman MN, Pearce BD, Biron CA, Miller AH. Immune modulation of the hypothalamic-pituitary-adrenal (HPA) axis during viral infection. Viral Immunol. 2005;18(1):41-78. DOI: 10.1089/vim.2005.18.41. PMID: 15802953; PMCID: PMC1224723.

30- Olson NC, Dobrowsky RT, Fleisher LN. Dexamethasone blocks increased leukotriene B4 production during endotoxin-induced lung injury. J Appl Physiol (1985). 1988 May;64(5):2100-7. DOI: 10.1152/jappl.1988.64.5.2100. PMID: 2839453.

31- Olson NC, Brown TT Jr, Anderson DL. Dexamethasone and indomethacin modify endotoxin-induced respiratory failure in pigs. J Appl Physiol (1985). 1985 Jan;58(1):274-84. DOI: 10.1152/jappl.1985.58.1.274. PMID: 3881383.

32- Hirai A, Tahara K, Tamura Y, Saito H, Terano T, Yoshida S. Involvement of 5-lipoxygenase metabolites in ACTH-stimulated corticosteroidogenesis in rat adrenal glands. Prostaglandins. 1985 Nov;30(5):749-67. DOI: 10.1016/0090-6980(85)90005-x. PMID: 3001830.

33- Toumpanakis D, Kastis GA, Zacharatos P, et al. Inspiratory resistive breathing induces acute lung injury. *Am J Respir Crit Care Med*. 2010;182(9):1129-1136. doi:10.1164/rccm.201001-0116OC

34- Cui X, Chen W, Zhou H, et al. Pulmonary Edema in COVID-19 Patients: Mechanisms and Treatment Potential. *Front Pharmacol*. 2021; 12:664349. Published 2021 Jun 7. doi:10.3389/fphar.2021.664349

35- Vassilakopoulos T, Toumpanakis D. Can resistive breathing injure the lung? Implications for COPD exacerbations. *Int J Chron Obstruct Pulmon Dis*. 2016; 11:2377-2384. Published 2016 Sep 26. doi:10.2147/COPD.S113877

36- Pappagallo M, Abbasi S, Bhutani VK. Respiratory and systemic effects of inhaled dexamethasone on ventilator dependant preterm infants at risk for bronchopulmonary dysplasia. *Indian J Pediatr*. 1998;65(2):273-282. doi:10.1007/BF02752304

37- Yoder MC Jr, Chua R, Tepper R. Effect of dexamethasone on pulmonary inflammation and pulmonary function of ventilator-dependent infants with bronchopulmonary dysplasia. *Am Rev Respir Dis*. 1991;143(5 Pt 1):1044-1048. doi:10.1164/ajrccm/143.5_Pt_1.1044