Inflammation Links Stress to Poor COVID-19 Outcome

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Introduction

- Coronavirus disease 2019 (COVID-19), caused by SARS-CoV-2, leads to severe health outcomes in 20% of cases[1]
- Predisposing inflammatory mechanisms likely contribute to susceptibility to a worse COVID-19 prognosis
- Chronic stress, which elicits a sustained proinflammatory response, might interact synergistically with this virus, producing fatal outcomes
- SARS-CoV-2 produces similar pathology to that of chronic stress:
  - Direct cytopathic effect on adrenal cells[2]
  - Elevated serum cortisol (CORT) concentration[3]
  - Simultaneous activation of helper T cell type-1 (TH1) and TH2[4]
  - T lymphopenia, leading to necrosis of the thymus gland[5]
  - Hyperactivation of the nuclear factor kappa B (NF-κB) pathway, initiating a cytokine storm; namely, interleukin-6 (IL-6) hypersecretion[6]
- Further research is required to understand the compounded effects of SARS-CoV-2 with chronic stress

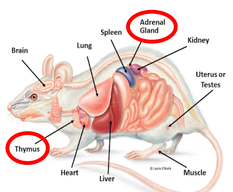
Methods

We examined overlapping pathology between stress and SARS-CoV-2:

CHRONIC MILD STRESS (CMS):
Twenty-four male Wistar rats (postnatal day (PD) 49) were randomly assigned to either a no stress control (CTL) (*n*=12) or CMS (*n*=12) condition. During the 21-day CMS period[7], CMS rats were continuously exposed to a variety of stressors (e.g., cage tilt, water deprivation).

Following CMS, rats were left undisturbed for a 60-day recovery period until adulthood (PD 130). Then, we measured changes in:

- ❖ Adrenal gland weight
- ❖ Thymus gland weight
- ❖ Plasma IL-6 concentration
- ❖ Central cannabinoid receptor 2 (CB2) expression



Results

Hypercytokinemia in SARS-CoV patients and chronic stress-exposed individuals

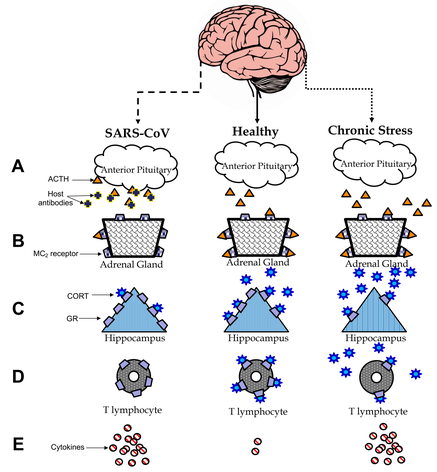


Figure 1. **Differential processes contribute to hypercytokinemia in SARS-CoV patients and chronic stress-exposed individuals**.

(A) The anterior pituitary gland releases adrenocorticotropic hormone (ACTH). In SARS-CoV patients, the virus mimics ACTH, causing host antibodies to destroy endogenous ACTH.

(B) ACTH binds to its receptors in the adrenal cortex, stimulating the production of glucocorticoids, namely, cortisol (CORT). Due to insufficient bioavailability of ACTH, SARS-CoV leads to less adrenal CORT production.

(C) CORT binds to glucocorticoid receptors (GR) in the hippocampus, which suppresses further release of glucocorticoids from the adrenal glands. Chronic stress causes GR downregulation, impairing the ability of the hippocampus to regulate CORT secretion and leading to hypercortisolism.

(D) In SARS-CoV patients, insufficient CORT is available to bind to GRs whereas in chronic stress, there is an abundance of CORT with few receptors available to bind. Under normal conditions, CORT inhibits immune cells, like T lymphocytes, thereby leading to **(E)** suppression of inflammatory responses, namely proinflammatory cytokine release. In SARS-CoV patients, decreased CORT bioavailability promotes unrestrained cytokine release. Similarly, in individuals experiencing chronic stress, GR downregulation in immune cells prevents CORT from suppressing the inflammatory response, leading to hypercytokinemia.

Interleukin 6 (IL-6) correlates with adrenal hypertrophy and thymus involution after early adversity

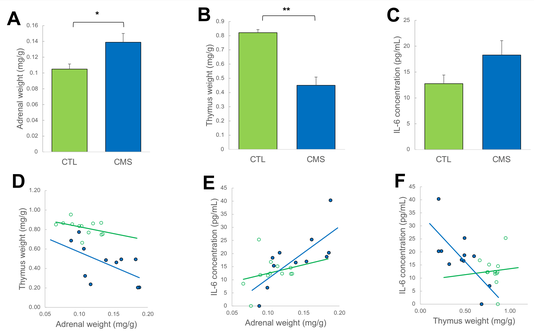


Figure 2. Top panel shows **(A)** adrenal weight per body weight (mg/g), **(B)** thymus weight per body weight (mg/g), and **(C)** plasma IL-6 concentration (pg/mL) in control (CTL) and chronic mild stress (CMS) animals. Bottom panel shows relationships between **(D)** thymus and adrenal weight, **(E)** IL-6 concentration and adrenal weight, and **(F)** IL-6 concentration and thymus weight in CTL (open circles, green line) and CMS (solid circles, blue line) rats. Data are presented as group means and error bars represent standard error of the mean (SEM). (*) denotes statistical significance, $p<.01$, (**) denotes $p<.001$.

Early adversity upregulates cannabinoid receptor 2 (CB2) expression in the brain

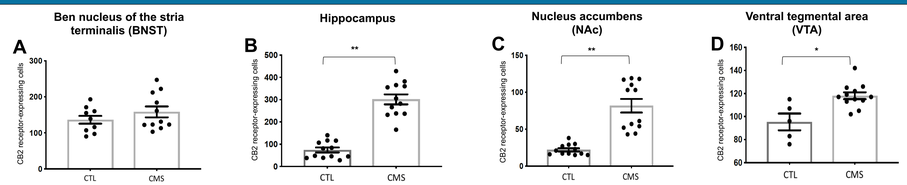


Figure 3. Bars represent cell counts of immunoreactive cells expressing CB2 receptors in the **(A)** bed nucleus of the stria terminalis (BNST), **(B)** hippocampus, **(C)** nucleus accumbens (NAc), and **(D)** ventral tegmental area (VTA) of control (CTL) and chronic mild stress (CMS) animals. Data are presented as group means and error bars represent standard error of the mean (SEM). (*) denotes statistical significance, $p<.01$, (**) denotes $p<.0001$.

Conclusions

- Chronic stress produces sustained inflammatory responses, as well as adrenal and thymus gland atrophy
- These findings overlap with SARS-CoV-2-induced pathology, suggesting these responses could synergize
- Prior history of chronic stress should be considered a significant risk factor for adverse COVID-19-related health outcomes
- We present novel insight into the role of CB2 receptors as a potential therapeutic target to restrain the hyperinflammatory response in COVID-19 patients

Risk Mitigation

- Given that several mental health conditions (e.g., depression) are precipitated by chronic stress, stress-reduction strategies are critical for these individuals
- Practice mindfulness meditation, which modulates CORT and reduces inflammatory responses[8], promoting better viral immunity
- Follow physical (as opposed to social) distancing by using online platforms to promote social bonding
- Make use of internet-based therapy (e.g., iCBT), which provides emotional support that is as effective as in-person support for emotion regulation[9]

References
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