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 cytokopathic 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.6
  - Hyperactivation of the nuclear factor kappa B (NF-κB) pathway, initiating a cytokine storm; namely, interleukin-6 (IL-6) hypersecretion.8
- 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, 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

Chronic stress causes GR downregulation, impairing the ability of the hippocampus to regulate CORT secretion and leading to hypercortisolism. 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 the 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 responses, leading to hypercytokinemia.

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

Inflammation Links Stress to Poor COVID-19 Outcome

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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, 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., ICTB), which provides emotional support that is as effective as in-person support for emotion regulation.

References

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