Review

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Review

Proposing Bromo-epi-androsterone for Neurologic Long-COVID

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Abstract: The neurologic effects of long-COVID are a therapeutic challenge. This article discusses the immunologic manifestations of long-COVID and proposes a non-androgenic, synthetic analog of dehydroepiandrosterone (DHEA), bromo-epi-androsterone (BEA), as a candidate for clinical trials for this exigent collection of neurologic conditions. Moreover, because there is an association between long-COVID and Alzheimer's disease, the evaluation of BEA in long-COVID may serve as a proxy for its effect on neuroinflammatory biomarkers of Alzheimer's disease that are shared with long-COVID.

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1. Introduction

The Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) is the pathogen responsible for COVID-19 disease; when COVID symptoms persist, the condition is commonly referred to as long-COVID. Multiple mechanisms are thought to contribute to the multisystem manifestations and prolonged symptoms experienced in long-COVID cases. This article addresses neurologic aspects of long-COVID and how immune dysregulation is thought to participate in these manifestations. Moreover, the article proposes the utility of the synthetic dehydroepiandrosterone (DHEA) analog, bromo-epi-androsterone (BEA), as a multi-faceted intervention to promote immune homeostasis and reduce non-productive inflammation resulting in a favorable outcome to this disease.

Current research suggests the pathogenic mechanisms underlying long-COVID include the persistent presence of SARS-CoV-2 virus [1], formation of microscopic blood clots [2], dysregulation of the immune system [3], disruption of normal mitochondrial function including mitochondrial "storms" [4], reactivation of latent viral pathogens such as the Epstein-Barr virus and human herpesvirus-6 [5], extension of ongoing inflammatory processes [6], triggering of autoimmune responses [7], as well as impairment of brainstem signal transduction pathways and dysfunction of vagus nerve signaling [8,9].

2. COVID and Cognitive Dysfunction

COVID-19 infection frequently leads to persistent cognitive dysfunction commonly known as "brain fog." This condition involves impairments in attention, processing speed, memory, and executive functioning [10]. Symptoms including fatigue, sleep problems, language difficulties, and loss of smell/taste frequently accompany brain fog [11]. Meta-analyses indicate that around 22% of COVID-19 patients experience cognitive dysfunction 19 weeks after infection, with nearly 20% still affected at 9 months [12,13]. Both mild and severe COVID-19 cases can result in prolonged cognitive impairment, which worsens the longer the symptoms persist [14].

The apparent primary driver of COVID-19-related cognitive decline is the extended inflammation triggered by SARS-CoV-2 infection. This inflammation can increase blood-brain barrier permeability, activate brain immune cells like microglia and astrocytes, and ultimately lead to

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neuronal damage [15,16]. The virus can also invade and damage dopamine neurons in the midbrain, which is implicated in Parkinson's disease [17]. Chronic inflammation reduces neurogenesis and impairs synaptic plasticity in the hippocampus resulting in memory deficits. Furthermore, inflammatory factors can disrupt mood regulation, causing depression and other mood issues in survivors [18].

3. COVID and Immune Dysregulation

SARS-CoV-2 infection triggers both the innate and adaptive immune responses to clear the viral pathogen [19]. However, in patients with long COVID, there are observed changes in immune cells, increased autoantibody levels, and reactivation of latent viruses *[20–22]*. The long-term effects of COVID-19 on the immune system are evident through epigenetic and transcriptional alterations in monocytes, which can lead to chronic inflammation, excessive autoimmune activity, and persistent consequences throughout the body [23].

Recovering COVID-19 patients exhibit abnormalities in intermediate monocytes and T-cell activation, associated with ongoing endothelial cell activation and coagulation dysfunction [24,25]. Long COVID patients show a decline in CD4+ and CD8+ effector memory cells [26], while pro-inflammatory cytokines like IFN-β and IFN-λ1 remain elevated for several months after infection [27]. The persistent SARS-CoV-2 presence also leads to dendritic cell deficiency [28] and reductions in non-classical monocyte and lymphocyte subsets [29].

This aberrant and sustained immune activation produces a broad spectrum of self-targeting antibodies hypothesized to contribute to various long COVID symptoms [30]. Long-COVID patients exhibit abnormally high levels of functional autoantibodies targeting G protein-coupled receptors linked to both persistent neurological and cardiovascular issues [31]. SARS-CoV-2-induced autoimmunity can cause immune blood disorders, antiphospholipid syndrome, systemic lupus erythematosus, vasculitis, acute arthritis and Kawasaki-like syndromes [32].

Neurological complications of long COVID are also associated with changes in inflammatory cytokines. Interleukin-6 (IL-6) levels are significantly increased in patients with Long-COVID compared to those without post-Covid symptoms *[33,34*]. Indeed, high IL-6 levels are associated with both development and severity of Long Covid neurological manifestations [35].

Although not looking at neurologic complications specifically, Long-COVID patients have elevated IL-1β, TNF and IP-10 cytokines [36]. Interferon-alpha (IFN-α) levels are also elevated in Long-COVID patients, particularly those with neurological symptoms [34]. Activation of the cGAS-STING pathway, which induces IFN-α production, may contribute to neurodegenerative processes in Long-COVID [34]. The anti-inflammatory cytokines IL-4 and IL-10 are reduced in Long-Covid patients compared to those without post-Covid symptoms, suggesting an imbalance that favors a pro-inflammatory state that could drive neurological complications [33,36].

4. DHEA and Cortisol

DHEA (dehydroepiandrosterone) and its sulfate (DHEA-S) are the most abundant steroids of the metabolome and play essential roles in physiological processes such as metabolism, immune function and the stress response [37]. The DHEA secretory rate changes throughout an individual's lifespan; after attainment of adulthood levels that plateaus until the late 20's, DHEA levels start a steady decline such that by 70-80 years of age, peak concentrations of DHEAS are only 10-20% of those in young adults [38].

DHEA and cortisol have opposite hormonal actions and the balance between DHEA and cortisol levels is important for multiple and diverse physiologic functions [39]. DHEA is known as the "youth hormone" [41]; and cortisol is commonly known as the "stress hormone" [42]. A lower DHEA to cortisol ratio is associated with stress, metabolic syndrome, immune dysfunction including susceptibility to infection, frailty and all-cause mortality [43–47]. While the adrenal glands are the primary site for these steroids, they are also locally synthesized in other tissues including primary lymphoid organs, intestine, gonads, skin, brain and the heart [48]. The age-related decrease in the DHEA/cortisol ratio is associated the with immunological changes observed during ageing,

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immunosenescence [49,50] along with the paradoxical concurrent upregulation of inflammation, inflammaging[51].

5. BEA – (16 Alpha-bromoepiandrosterone)

BEA (16 alpha-bromoepiandrosterone) is a synthetic DHEA analog that lacks DHEA's androgenic and estrogenic actions. A primary mechanism of DHEA is as a potent inhibitor of mammalian glucose-6-phosphate dehydrogenase (G6PDH); and in this regard, BEA is about 60 times as potent as DHEA [52]. A previous formulation of BEA was developed over 20 years ago as a treatment for a range of human infections; in 9 clinical trials, that formulation treated 228 participants for varying infections: HIV, malaria and hepatitis *[53–55*].

In March of 1999, the FDA issued an IND (investigational new drug) status for this formulation to be investigated in patients with HIV/AIDS [56,57] for which it showed efficacy [58]. Since BEA limits non-productive inflammation [59] and exhibits broad immune support, it has been proposed as a treatment for the world's greatest pathogen Mycobacterium tuberculosis [60,61].

Like DHEA, BEA promotes a T1 response [62] and rebalances the Th1/Th2 ratio that naturally decreases with age; this offsets the consequences of a Th2 shift: increased susceptibility to infections, reduced response to vaccines, and higher incidence of autoimmune disorders in the elderly *[63–65*].

6. Discussion

Significant immune differences between individuals with long-COVID and controls are distinguished by circulating immune cell populations [22]; this gives reason to believe that restoring immune homeostasis with an agent such as BEA would benefit the inflammatory state associated with this immune dysregulation and lead to improvement in long-COVID symptoms. Identifying and implementing tools for neuropsychologic assessment will be imperative to accurately assess a treatment effect for BEA or other proposed therapeutic interventions for neuro-long-COVID *[66–68*].

Brain changes seen in Alzheimer's disease (AD) overlap with those observed in COVID-19 patients with the conditions sharing similar biologic pathways [69]. Cognitive changes associated with long-COVID are also associated with Alzheimer's disease *[70,71*] with common processes of neuroinflammation and cerebral microvascular injury [72]. Interferon 1 (IFN-1) signaling has been offered as a plausible mechanism of cognitive impairment in both long-COVID and AD [73]. In 2022, a collaborative international task force formed by the WHO and the Alzheimer's Association published a protocol to systematically investigate the neuropsychiatric aftereffects of COVID infection. Noting that the SARS-CoV-2 virus can directly infect the brain, they also provided a review of the evidence connecting those COVID manifestations to Alzheimer's disease and related dementias (ADRD). Their specific hypothesis is that "SARS-CoV-2 induces ADRD-like pathology along the extended olfactory cortical network (EOCN) in older individuals with certain genetic susceptibilities;" the involvement of the olfactory cortical network in early AD is well established, and olfactory dysfunction is a strong clinical correlate of mild cognitive impairment (MCI) in AD and other dementias [74]. Theories supportive of a causative role for infectious agents in AD are not novel [75]. A molecular mechanism for SARS-CoV-2 cerebral involvement involves human angiotensin-converting enzyme 2 (ACE2) receptors, abundantly expressed in the brain and olfactory bulb *[76,77*], are sites of the SARS-CoV-2 invasion [71].

Anticipating a clinical trial of BEA for the neurologic complications of long-COVID with the understanding that this disease may be considered a surrogate for AD, a range of traditional and novel inflammatory markers could be employed as outcomes to assess BEA intervention as it relates to both diseases. Monitoring BEA's influence on the neurologic effects long-COVID may provide insights into AD management with BEA's impact on neuroinflammation in long- COVID serving as a proxy for AD treatment efficacy. The range of blood-based markers would include CRP, IFN, TNF, IL-1b, IL-2, IL-5, IL-6, IL-10, IL-17, NLRP3, GM-CSF, CXCL9, CCL-11, Klotho, MCP-1, BDNF, GFAP, LPC, NFL, HGS, 5-CSt, Lumican, Cortisol, LTL (leukocyte telomere length) and CD38.

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7. Summary

The manifestations of post-acute sequelae of SARS-CoV-2 virus infection in a large database of the US Department of Veterans Affairs identified over 150,000 neurologic long-COVID cases from a cohort of over 5 million contemporary controls and over 5 million historical controls [78]. An abundant database such as this with a well characterized population may provide ample opportunity for assessing the value of BEA in neurologic long-COVID and, by extension, Alzheimer's disease.

Conflicts of Interest: The author serves as the Chief Medical Officer for Protibea Therapeutics, Inc.

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