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Perspective

The Curse of Geography: On Latitude and Suicidal Behavior

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We read with great interest the article "Global prevalence of suicide by latitude: A systematic review and meta-analysis" by Seongjun An, published in the Asian Journal of Psychiatry on January 7, 2023. In this work, the authors examine numerous studies from 1982 to 2020, demonstrating that the worldwide prevalence of suicide increases with the distance from the equator. The authors concluded that low vitamin D levels caused by insufficient sunlight exposure likely affect the central nervous system (CNS) myelin repair, contributing to higher suicide rates.

The relationship between climatological factors and suicide has been highlighted by the earlier studies however, arrival of COVID-19, an infection with the SARS-CoV-2 virus, has put this correlation in proper perspective [1-4]. For example, COVID-19 mortality rates were found to be lower south of the latitude 35 degrees North, connecting recovery from this infection with the availability of aryl hydrocarbon receptor (AhR) ligands, tryptophan photooxidation products and vitamin D [5-8]. In this regard, as SARS-CoV-2 and several other viruses activate AhR, antagonists of this receptor likely exert antiviral properties [9,10]. Moreover, tryptophan photoproducts and calcitriol, the active form of vitamin D3, may possess both antiviral and antidepressant actions, accounting for the elevated suicide rates and increased SARS-CoV-2 mortality at higher latitudes [7,11]. For example, the anti-suicidal properties of clozapine, an AhR ligand and reserve antipsychotic drug, are well-established, linking this receptor to suicidal behavior [12]. Along these lines, since serotonin, melatonin and gut microbiota-derived tryptophan metabolites are AhR ligands, this receptor has emerged as a potential neuropsychiatric target [13]. Moreover, AhR is an integral part of circadian clock, the internal molecular machinery that regulates sleep–wake cycle, suggesting that it may

function as a sunlight sensor, maintaining the homeostasis of excitatory and inhibitory CNS pathways via serotonin and melatonin [14,15]. Since suicidal behavior has been associated with dysfunctional circadian clock, AhR signaling likely plays a key role in the pathogenesis of major depressive disorder (MDD), multiple sclerosis (MS), and schizophrenia [16,17].

In the following sections of this commentary, we take a closer look at the role of climatological factors in neuropathology, including suicide. Moreover, we highlight the role of AhR as a receptor for solar electromagnetic radiation, as well as a potential druggable target for MDD, suicidal behavior, and schizophrenia.

Suicide and AhR

Suicide is the second leading cause of mortality in adults, contributing worldwide to more than 800 000 deaths per year [18]. Despite improvement in MDD treatments over the past decade, the incidence of suicidal behavior has remained largely unaffected. In fact, it has increased in adolescents and is currently the third leading cause of death in this group [19].

Studies over the past four decades have implicated various tryptophan metabolites in suicide, including 5-hydroxyindoleacetic acid (5-HIAA), however, the relationship of these molecules to AhR and sunlight was poorly defined [20].

In the gut, tryptophan is absorbed via broad neutral amino acid transporter 1 (B0AT1), a protein that dimerizes with angiotensin converting enzyme 2 (ACE-2), the entry portal of SARS-CoV-2 virus. When the virus occupies ACE-2, tryptophan absorption is impaired and AhR activated, disrupting the gut barrier through virus-induced premature endothelial senescence [21] (Fig. 1). This facilitates microbial translocation into the host systemic circulation and from there into the brain. Indeed, several studies have documented the existence of a brain microbiome, microorganisms that do not actively replicate in the CNS but thrive in a dormant state until the conditions for replication become favorable [21,22]. In this regard, microbial DNA as well as lipopolysaccharide (LPS), a component of Gram-negative bacteria, were detected in the brain of patients with Alzheimer's disease (AD), a neurodegenerative disorder more prevalent at higher latitudes [23-27]. Indeed, distance from the equator and low temperatures have been associated with the disruption of gut barrier and increased microbial translocation into host tissues [28]. Moreover, certain microbial species previously associated with suicide were found to exhibit latitudinal variation, likely accounting the increase of this pathology in northern countries [29,30]. For example, the myelin-mimicking proteins of Acinetobacter, a microbe thriving at higher latitudes, may explain the increased prevalence of both MS and suicide in those areas [31-33]. Furthermore, tryptophan depletion has been associated with increased suicide rates as the translocated microbes or their proteins activate the proinflammatory kynurenine (Kyn) pathway [34,35]. Indeed, reduced peripheral tryptophan and increased activation of Kyn pathway was demonstrated in MDD and suicidal behavior, linking these pathologies to inflammation [34,36].

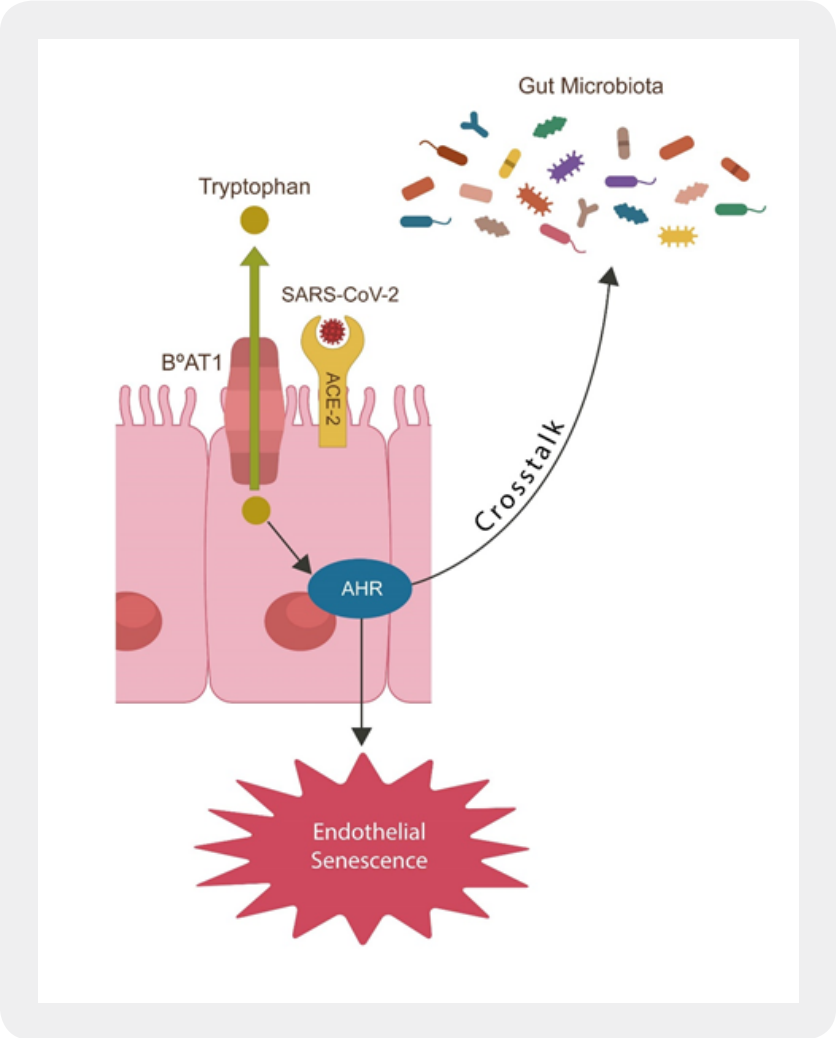

Figure 1: *ACE-2 dimerizes with tryptophan transporter, B0AT1. When SARS-CoV-2 virus attaches to ACE-2, it activates AhR, disrupting tryptophan absorption and causing premature endothelial senescence as well as microbial dysbiosis. Under normal circumstances AhR is inhibited by microbial tryptophan metabolites, however, dysbiosis prevents this from taking place. Endothelial senescence disrupts the gut barrier, enabling microbial translocation outside of the GI tract.*

Other Latitude-Dependent Disorders

Aside from neuropsychiatric disorders, the curse of geography also extends to several cancers, connecting excessive AhR activation with tumorigenesis. Inactive AhR resides in the cytosol however, when activated, it enters the nucleus, altering the expression of many genes that may lead to cell cycle pathology and malignant transformation. For this reason, inhibitory AhR ligands, including microbial metabolites, vitamin D, and tryptophan photoproducts are being evaluated as anticancer agents [37]. For example, breast cancer and colorectal carcinoma, are more prevalent in Northern countries, likely connecting this pathology to AhR

activation, while AhR inhibitors, such as BAY 2416964, are currently being developed as anticancer drugs [38-43].

Aside from affective disorders and suicide, the prevalence of several other neuropsychiatric conditions, including schizophrenia, autism spectrum disorders (ASD), and MS, is lower near the equator and increases at higher latitudes, implicating AhR activation in these pathologies [44-46]. Conversely, pyridopyrimidinone, a patented AhR antagonist, may represent the avantgarde of future neuropsychiatric treatments (WO-2021102288-A1) [47].

Microbial Translocation Outside the GI Tract

In our previous work on microbial translocation disorders, we discussed antibodies against gut microbes and/or their components that are often misconstrued as autoantibodies [48]. The distinction between the antibodies and autoantibodies is important to make as some drugs commonly used for treating autoimmune disorders, such as methotrexate, disrupt the gut barrier, promoting additional translocation of microbes [49]. Conversely, gut barrier repair likely comprises a key therapeutic strategy for autoimmune disorders. For example, Baicalein, a compound which optimizes gut barrier function, has been patented for autoimmune disorders, linking this pathology to microbial translocation (CN101491533B) [50].

Microbial translocation into the host systemic circulation likely connects neuropsychiatric disorders, autoimmunity, and cancer [51]. For example, the latitude-related autoimmune disorders, inflammatory bowel diseases (IBSs), were associated with increased rates of suicide, linking this pathology to dysfunctional gut barrier [52-54]. In addition, bacterial translocation markers, including circulatory LPS and intestinal fatty-acid binding protein (I-FABP), were found elevated in suicide attempters, connecting once again neuropathology to gut barrier disruption [55]. As commensal microbiota express proteins identical or similar to those of the human host, their translocation can activate the immune system, triggering pathology [56-59]. For example, Escherichia coli (E. coli) expresses glutamate receptors B and D (GluR-B and GluR-D), which upon translocation, could elicit anti-N-methyl-d-aspartate-receptor (NMDAR) antibodies, immunoglobulins previously associated with suicidal behavior [56,60]. Moreover, Bacteroides species and Pseudomonas fluorescens produce γ-aminobutyric acid (GABA) and GABA-binding proteins, which could elicit anti-GABA antibodies, molecules also connected to suicidal behavior [61,62].

Allergic Disorders and Suicide

A 2008 study by Postolache TT et al. found that several allergic conditions increase the suicide risk, linking this pathology to type II hypersensitivity [63-65]. In addition, as hypersensitivity reactions are more common at higher latitude, suicidal behavior in those areas may be due to combination of hypovitaminosis D and atopic phenotypes [66,67].

In 2010, mucosa-anchored group 2 innate lymphoid cells (ILC2s) were discovered, a local immune system implicated in anti-helminthic immunity as well as in the pathogenesis of allergic diseases, including asthma [68]. As ILC2 regulate oligodendrocytes and myelin generation, they were implicated in neuropathology,

including MDD and suicide [69-71]. Demyelinating disorders, such as MS or the related condition neuromyelitis optica, have been associated with increased suicidal behavior, connecting, type II hypersensitivity to these pathologies [72-75]. For example, upregulation of ILC2-associated interleukin-4 (IL-4) and/or IL-13, were implicated in suicide by earlier studies, further connecting this condition to dysfunctional myelin [76].

Mast cells (MCs), known for allergy-mediated histamine release in type I hypersensitivity, also participate in emotional regulation, and cognition, linking allergic reactions to neuropathology [77]. These cells have been known for forming extracellular traps (ET), also known as ETosis, a phenomenon involving externalization of antimicrobial peptides (AMPs), histone proteins, and DNA, upregulating the extracellular cell-free DNA (cfDNA), a marker of neuropathology, including suicide [78,79]. Interestingly, vitamin D inhibits NETosis, lowering cfDNA, revealing the antiallergic properties of this molecule [80,81].

Conclusions

Many human diseases have been associated with colder climate and higher latitude, indicating that insufficient sunlight, hypovitaminosis D and low tryptophan photoproducts likely contribute to these pathologies.

Tryptophan photooxidation and conversion of pre-vitamin D3 via UV radiation into the active vitamin D3 indicate that despite the separation of modern societies from nature, humans continue to depemd on the environment for survival.

Suicide, conceptualized as a pathology of insufficient sunlight exposure, is further proof that human biology is highly intertwined with the surrounding world and the universe. AhR, like chlorophyll in plants, functions as a liaison with the outer world, maintaining the photo-homeostasis of circadian, seasonal, and geographic changes. Therefore, a better understanding of AhR, the master regulator of geo-adaptation, will help design better treatments for mental illness, cancer and other poorly understood disorders.

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