The Potential Role of the Vagus Nerve in HIV-Associated Neurocognitive Disorders

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Theoretical Framework for HIV and Vagus Nerve

Introduction
HIV can infect the brain and impair central nervous system (CNS) function by influencing HPA-axis, microbiome, and inflammatory systems. HIV-associated Neurocognitive Disorders (HAND) can result from its influence on the health of nerve cells. HAND affects 52-59% of adults on combination anti-retroviral therapies with deficits in executive function, memory, speed of processing, attention, and psychomotor speed. Unfortunately, effective interventions for these populations are lacking. The vagus nerve mediates HPA-axis, microbiome, and inflammatory interactions. Its ability to maintain homeostasis through parasympathetic networks makes it an intriguing target for intervention. The purpose of this theory is to determine if HIV impairs the vagus nerve and disrupts homeostatic communication signals between the body and brain precipitating a chronic inflammatory state that contributes to HAND.

Vagus Nerve
• Cranial nerve X
• Major component of the autonomic nervous system that influences neuronal, endocrine, and immune functions.
• Maintains homeostasis by its afferent and efferent connections through bi-directional communication link between brain and gastrointestinal (GI) system (known as gut-brain axis).

Microbiota and Dysbiosis
• Microbiota refers to bacteria residing in the GI system (microbiome).
• Symbiotic relationship to host influencing systemic functions through gut-brain axis (e.g. cognition, immune response, etc.).
• Dysbiosis refers to pathogenic changes in microbiota resulting from HIV infection.
• Microbial translocation occurs during dysbiosis through weakened epithelial and mucosal barriers allowing pathogens to enter CNS.
• Entry stimulates pathogenic and chronic inflammatory response.

Hypothalamic-parietal-adenal axis (HPA-axis)
• Regulates adaptive stress response through endocrine, nervous, and immune system activation.
• Responds to increases in glucocorticoids (inflammation) in order to maintain cognitive and systemic homeostasis.
• Brain-derived neurotrophic factor (BDNF) regulates function of HPA-axis and is responsible for neuroplasticity.
• HIV deregulates HPA-axis creating chronic stress response that accelerates aging and contributes to neurodegeneration.

HPA-Axis with HIV:
• Impaired negative feedback
• Basal glucocorticoid levels
• Changes to hippocampus function and morphology
• Memory and cognitive impairments
• Accelerated aging
• Reduction in BNDF

Inflammation with HIV:
• Depleted CD4+ T-cells
• Cytokine production
• Microglial dysfunction

GI with HIV:
• Dysbiosis
• Weakened epithelial & mucosal barriers
• Microbial Translocation
• Pathogenic Microbiota
• gAδ-gut-neuroaxis
• Glutamate= neurotoxicity
• Serotonin= immune activity
• Inflammatory Cytokines= sustained stress response
• Kynurenic acid inhibiting acetylcholine receptors

Microbiota in HIV:
• Bifidobacterium
• Lactobacillus
• Decreases GABA production
• Decrease weaker immune response & epithelial integrity

Vagus Nerve:
• Inability to help regulate stress response
• Alterations in microbiotic reception, thereby changing output and response
• Alterations in neurotransmitter reception
• Reduced ability to provide acetylcholine

Vagus Nerve and HIV-associated Neurocognitive Disorders
• The vagus nerves afferent and efferent processes allow it to promote homeostasis during HIV-association, inflammatory, and microbiome instability.
• Vagal afferents transfer information through gut-brain axis (e.g., inflammatory signals) and are responsible for behaviors that include lethargy, depression, anxiety, loss of appetite, sleep disturbances, and cognitive disorders.
• The efferent vagal nerve pathways regulate GI, endocrine, neuronal, and inflammatory activity.
• Pathways utilize microbiota for medication and production of gamma-amino butyric acid (GABA) and glutamate helping regulate cognition.
• Pathways interact with microbiota and gut-brain axis to activate anti-inflammatory defense against pathogens.
• Efferent pathways reestablish epithelial and mucosal barrier integrity which provides protection against microbial translocation.
• Efferent response activates cholinergic anti-inflammatory pathway through immune cell interactions attenuating inflammation by production of acetylcholine (ACh).
• ACh's primary function is regulating cognitive and immune activity.
• HPA-axis dysfunction in HIV changes systemic utilization and storage of ACh which interferes with cognitive processing.
• HIV reduces BNDF through HPA-axis deregulation and dysbiosis.
• Vagus nerve increases BNDF production.
• BNDF production regulates excessive glucose released in response to stress and increased serotonin production.
• HIV dysbiosis breaks down tryptophan (serotonin precursor), increasing cytokine and kynurenic acid production.
• Kynurenic acid inhibits ACh pathways which deregulates glutamate, creating a neurotoxic state.
• Negative relationship exists between increase in kynurenic acid and cognition.
• Efferent pathways decrease kynurenic acid production and increase availability of tryptophan through ACh pathways.

HIV infected Vagus Nerve:
• Pathways to regulate neurotransmitter production
• Reducing ability to provide acetylcholine

Discussion
• HIV precipitates a chronic stress state by deregulating HPA-axis, microbiome, and immune systems.
• Deregulating these systems creates physiological instability that interferes with healthy cognition.
• Vagus nerve is a bi-directional conduit that responds to instability by activating the parasympathetic nervous system.
• The functionality of the vagus nerve is critical for endocrine, neuronal, and immune responses to invading pathogens.
• If HIV the impairs vagus nerve then it increases its chance of survival in the host by avoiding natural defense systems.
• The impairment of the vagus nerve disrupts communication interfering with the brain/body’s ability to regulate systems.
• Stimulation of the vagus nerve could help reestablish brain/body communication and stabilize cognitive function.
• Furthermore, the addition of “biotics” could stimulate a complete vagal response in the presence of HIV by altering pathogenic microbiota into a healthier composition helping restore communication and homeostatic function.

Hypothesized Study Design
• Recruit a sample of adults with HIV experiencing HAND.
• Obtain 4 Transcutaneous vagus nerve stimulating devices (tVNS) to function as intervention while improved or stabilized cognitive impairment will function as dependent variable.
• tVNS stimulation will be calibrated at 0.4 milliamperes (mA), with 30 seconds of stimulation, and 5 minutes without at 20 Hz for 1 minute (mA) per 0.5 millisecond (µs).
• Participants will be asked to perform self-stimulation for one hour everyday for 6 months to 1 year.
• Cognitive and task performance measures can be administered at baseline and post-stimulation trial (6 months to 1 year) to evaluate improvements.

References