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Biological Barriers and Severe Mental illness: Potential Novel Interventions

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Abstract

Life is dependent on the separation of body compartments from each other and the environment. The permeability of biological barriers, including the gastrointestinal and blood-brain, depends on the integrity of cell membranes and intercellular tight junctions.

Severe mental illness is characterized by premature cellular senescence and subsequent gray matter loss in the central nervous system. Senescence-induced gut barrier disruption enables microbial migration outside the gastrointestinal tract. Systemic immune responses to gut microorganisms or their molecules may lead to neuroinflammation and the subsequent pathology.

This review discusses cellular senescence and microbial migration outside of the gastrointestinal tract along with potential strategies for restoring the gut barrier homeostasis. These approaches include membrane lipid replacement, gamma wave entrainment, red light therapy, and pulsed electromagnetic field therapy.

Keywords: gut microbes; Membrane Lipid Replacement; Oscillations; EEG gamma waves; severe mental illness.

Introduction

Life depends on the integrity of biological barriers, beginning with the cell membranes that separate the human body from the outside environment and the barriers that separate tissues and organs from each other.

Biological barrier homeostasis is of utmost importance as its disruption was demonstrated in many diseases, including severe mental illness (SMI). Aryl hydrocarbon receptor (AhR), a transcription factor abundantly expressed at the gut and blood-brain barrier (BBB), is the master regulator of both tight junctions (TJs) and cellular senescence, thus controlling both molecular aging and barrier permeability (1)(2). Conversely, dysfunctional AhR allows gut microbes to migrate through the paracellular spaces in-between intestinal epithelial cells (IECs), accessing the systemic circulation and reaching the brain. Dysfunctional TJs and premature cellular senescence were demonstrated in patients with SMI and inflammatory bowel disease (IBD), implicating AhR in these pathologies (3)(4). Indeed, patients with schizophrenia (SCZ), known to live 15-20 years less than the general population, exhibit shorter telomeres, a more porous BBB, and higher prevalence of IBD (5)(6). Since mitochondria express mitochondrial AhR (mAhR), aberrant activation of this receptor may lead to the elimination of healthy organelles, a phenomenon documented in both SCZ and cellular senescence (7).

Dysfunctional AhR can contribute to premature molecular aging in IECs, further increasing microbial translocation. Moreover, impaired AhR may respond aberrantly to microbial molecules, such as tryptophan catabolites, shifting the processing of this amino acid toward kynurenine and quinolinic acid associated with SCZ, autism spectrum disorder (ASD), major depressive disorder (MDD), posttraumatic stress disorder (PTSD), and suicide (8)(9). Interestingly, psychological stress has been shown to increase microbial translocation by disrupting indoleamine dioxygenase (IDO), an essential tryptophan catabolizing enzyme, known for promoting immunological tolerance. Furthermore, microbe-activated AhR, and premature cellular senescence are known to drive lipid peroxidation, plasmalogen depletion, and toxic ceramide formation in cell membranes, hastening neuronal demise.

Membrane lipid replacement (MLR) and plasmalogen replacement therapy (PRT) can remove oxidized phospholipids from plasma and mitochondrial membranes, re-placing them with healthy, natural phospholipids, preventing neuronal senescence and gray matter volume loss (Fig. 1). Electric, magnetic, and sound stimulation of Vagus nerve and/or spleen may further lower the permeability of biological membranes, preventing neuropathology.

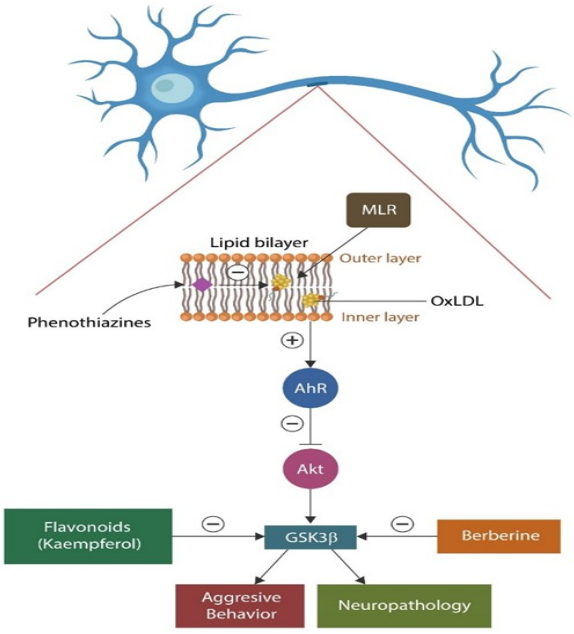

Figure 1. Neuronal cell lipid bilayer contains phospholipids, glycolipids, plasmalogen, and cholesterol. Oxidized lipids disrupt the cell and mitochondrial membranes, while pheno-thiazines exert antioxidant properties that can repair membrane lipids. This averts AhR activa-tion and the downstream GSK3β-mediated pathology. Two natural remedies, Kaempferol and Berberine, inhibit GSK3β, acting in synergy with lithium and some antipsychotic drugs.

Schizophrenia and dysfunctional cell membranes

A growing body of evidence suggests that membrane lipids, such as phosphatidylcholine (PC), phosphatidylethanolamine (PE), and plasmalogens, are significantly downregulated in patients with SCZ (10)(11). Lowered membrane lipids decrease fluidity and increase oxidative stress have been documented in SCZ (12).

Mitochondria contain a unique microbe-like double membrane structure, highlighting its likely bacterial origin. The membrane consists of an inner and outer leaflet, an intermembrane space, and a matrix containing mitochondrial enzymes, ribosomes, and mitochondrial DNA (mtDNA). The inner membrane harbors the electron transport enzymes involved in oxidative phosphorylation (OXPHOS). Like plasma membranes, the mitochondrial membrane contains an asymmetric lipid bilayer comprised of PE, cardiolipin (CL), and PC. CL is a unique lipid found primarily in the mitochondrial inner membrane that is crucial for maintaining the inner membrane fluidity and the transmembrane potential. In the CNS, CL is found in neurons and glial cells, where it maintains the energy homeostasis and drives damaged cells' apoptosis. Interestingly, anti-cardiolipin antibodies were documented in SCZ, while commensal gut flora, including *Muribaculum intestinale*, produces CL, suggesting that upon translocation, host antibodies may be directed at this microbe and not the mitochondrion itself (13).

Mitochondria contain mAhR that can be aberrantly activated by oxidized lipids, causing organelle demise. Excessive reactive oxygen species (ROS) can cause mem-brane damage, leakage of protons across the inner membrane, impaired ATP production, and cell death. For example, oxidized lipid-activated mAhR can drive glycogen synthase kinase 3 beta (GSK3β), a known SCZ pathogenetic mechanism (14)(Fig. 1).

Cellular and mitochondrial membranes exhibit asymmetric lipid bilayers marked by different lipidomes in each leaflet. For example, sphingomyelin is much more predominant in the outer leaflet, whereas PE and PS are predominantly located in the inner leaflet. The lipid asymmetry drives the physiological properties of cell membranes and their functional characteristics, including signal transduction, temperature adaptation, endocytosis, and apoptosis (15)(16). Conversely, loss of membrane asymmetry may lead to mitochondrial demise, a pathology described in SCZ. Membrane Lipid Replacement (MLR) refers to restoration of physiological membrane lipid composition to reverse pathology (17)(18).

Recent SCZ studies have linked dysmetabolism and obesity to reduced mitochondrial number, likely explaining the overall metabolic slowdown documented in this condition. Along this line, impaired mitochondrial fission, a process equivalent to microbial binary fission, reduces mitochondrial number and metabolism, a key characteristic of obesity and insulin resistance (19)(20)(21). Since metabolic dysfunction and cellular senescence co-occur, this program may contribute to both SCZ pathogenesis and dysmetabolism (22)(23)(24)(25).

When iron and fat get together

Cellular and mitochondrial lipid bilayer is susceptible to oxidation that can trigger cellular senescence, which may reflect a defense mechanism against ferroptosis (26, 27). Indeed, senescent cells upregulate intracellular iron, increasing the risk of

ferroptosis, a programmed cell death triggered by lipid peroxidation. Peroxidation-disrupted neuronal membranes can alter the biophysical properties of surface receptors, disrupting neurotransmission (Fig. 2).

Oxidized membrane lipids, especially sphingolipids, have been directly correlated with the vulnerability to mental illness and metabolic syndrome, suggesting that ferroptosis may play a significant role in these pathologies (28)(29). Together, this emphasizes once again the role of dysfunctional lipidome in neuropsychiatric disorders and metabolic syndrome. Indeed, increased ceramide and reduced mitochondria number have been documented in SCZ and insulin resistance, linking once more neuropathology to dysmetabolism (30)(31). Since ceramide is known for tagging defective mitochondria for mitophagy, it has been hypothesized that excess ceramide may contribute to the aberrant elimination of healthy mitochondria (32). Moreover, ceramide has been implicated in neuronal autophagy, a process in which microglia aberrantly engulfs and digests healthy neurons (33). This may explain why most patients with SCZ exhibit low white matter levels of phosphatidylcholine (PC) and high ceramide levels (34). Moreover, these findings suggest that correcting membrane lipidomes via MLR and PRT could ameliorate the SCZ outcome.

Ceramides are cell membrane phospholipids (composed of sphingosine and fatty acids) that play a key role in many cellular events, including growth, cell cycle, migration, autophagy, and response to stressors (35)

Under physiological circumstances, ceramides are obtained from three sources: the diet, de novo synthesis in human tissues, and production by gut commensal flora, such as *Bacteroidetes spp.* Along this line, the oral cavity *Bacteroidetes*, more abundant in patients with SCZ than healthy controls, emphasize the likely origin of ceramide (36). Moreover, several studies have shown that inflammation can convert ceramide into a toxin, leading to neuropathology, likely connecting this lipid to the neuroinflammation in SCZ (37). For example, novel preclinical studies have shown that gut microbes can metabolize dietary PC into a toxin, trimethylamine-N-oxide (TMAO), a biomolecule implicated in atherosclerosis, and SCZ (38). This is important not only for explaining the lower levels of PC in SCZ but also the high prevalence of coronary artery disease in people with this disorder (39). Indeed, proinflammatory cytokines and inflammation likely account for the presence of TMAO in SCZ and metabolic disorders. Indeed, earlier studies have shown that inflammation drives the formation of toxic ceramide species, resulting in CNS pathology, insulin resistance, and oxidative stress (39) (40).

Plasmalogens are a class of cell membrane glycerophospholipids with powerful antioxidant properties, including the ability to protect the membrane bilayer from peroxidation, a pathology documented in SCZ, Alzheimer's disease (AD), and metabolic syndrome (41). Asymmetrically displayed glycerophospholipids help maintain the biophysical properties of neuronal membranes, including their shape, fluidity, and thickness to stabilize membrane proteins, including cell surface receptors.

Phenazines and phenothiazines

Antipsychotic drugs with antioxidant properties, such as phenothiazines, were demonstrated to enter the lipid bilayers of cellular and mitochondrial

membranes, and repair the structural lipids (42)(43) (Fig.2).

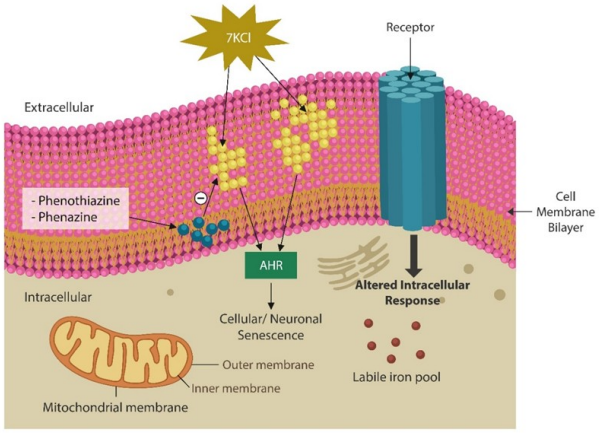

Figure 2. Natural phenazines and synthetic phenothiazines can ingress cell membrane lipid bilayer, reversing the oxidative damage caused by oxidants, such as 7-Ketocholesterol (7-KCl), preventing AhR activation. Toxic oxides alter the biophysical structures of membranes, altering neurotransmission by misaligning the surface receptors. Increased intracellular free iron in the presence of damaged lipids increases the risk of ferroptosis.

Indeed, reduced phospholipids in plasma membranes and platelets of patients with SCZ, mood disorders, and dysmetabolism are considered biomarkers of SMI and metabolic syndrome (44)(45)(46).

Naturally occurring phenazines, a class of phenothiazines produced by the marine and terrestrial microorganisms as well as by some gut microbes, can also act on neuronal membranes, likely comprising an inbuilt antipsychotic system, akin to the analgesic endogenous opioids. In addition, these agents exert antimicrobial, antiparasitic, neuroprotective, anti-inflammatory, and anticancer activities and are currently in clinical trials for these pathologies (42). At present, there are over 100 natural phenazines and about 6000 synthetic derivatives with antioxidant properties that can ingress cell membranes, protecting the lipid bilayer against peroxidation (42). Moreover, there are important new phenothiazines with strong antioxidant properties, that have been developed for cancer treatment, such as azaphenothiazines, that can be utilized in SCZ along with PRT or MLR (table 1).

Azaphenothiazines are modified phenothiazine compounds with antipsychotic and antioxidant properties that may be utilized in many conditions including psychosis and cancer. Biochemically, the benzene ring of phenothiazines is replaced in azaphenothiazines with one or more azine rings, resulting in: Monoazaphenothiazines: contain a single azine ring fused to the phenothiazine core. Diazaphenothiazines: contain two azine rings Triazaphenothiazines: three azine rings. Tetraazaphenothiazines: four azine rings. Azaphenothiazines can also be categorized based on the type of azine ring fused to the phenothiazine system. These include: Pyridobenzothiazines: fused with pyridine ring. Diazaphenothiazines (Dipyridothiazines): fused with two pyridine rings. Quinolinobenzothiazines: fused with quinoline. Other azaphenothiazine derivatives contain pyridazine, pyrimidine, pyrazine, 1,2,4-triazine, quinoxaline, benzoxazine, and benzothiazine rings. Biological activity: anti-inflammatory, hematopoietic, osteoclastogenic, neurogenic. It also has an influence on women's fertility and promotes development of T-cell-stimulated Ig-producing B cells. Some azaphenothiazines, including 10H-1,9-diazaphenothiazine and 10H-3,6-diazaphenothiazine, exhibit antitumor activity. Others are neuroprotective through various mechanisms, including free radical scavenging, anti-inflammatory effects, and autophagy induction. Many azaphenothiazines exhibit antipsychotic activity, including: prothipendyl and 1-Azaphenothiazine. These agents function as electron donors and prevent gray matter volume loss.

Table 1. Azaphenothiazines as the largest group of modified phenothiazines with antioxidant properties.

Cellular senescence and microbial translocation

SCZ is characterized by accelerated aging, shorter lifespan, decreased telomere length, and early onset of age-related diseases, indicating the involvement of cellular senescence, a program likely driven by AhR. Senescent cells arrest proliferation, re-wire their metabolism to protect against carcinogens and other endogenous or exogenous toxicants, and release a toxic secretome known as senescence-associated secretory phenotype (SASP) that can spread senescence to the neighboring healthy cells. Senes-cent IECs disrupt the gut barrier, leading to increased microbial translocation, and systemic inflammation (47). Indeed, the movement of microbes across the intestinal barrier, can promote inflammation by upregulating the levels of toxic ceramide (48).

Mitochondrial lipidome and rapid EEG frequences

Premature cellular senescence can occur in response to mitochondrial damage, impaired OXPHOS, and production of excessive ROS (49). Reduced mitochondrial number in neurons have been associated with the loss of EEG gamma waves (30-100Hz), frequences associated with cognition and higher intellectual functions (50).

The role of oscillations and vibrations in nature has been appreciated for thousands of years. For example, Pythagoras and his followers thought that celestial bodies vibrated in a musical rhythm. Nikola Tesla envisioned a universe governed by oscillatory frequencies, while in our time, two separate groups detected Universe-generated acoustic oscillations (51). Moreover, an Italian study found that 432 Hz tuned music can decrease heart rate, blood pressure, and respiratory rate compared to other frequencies (52). Others found that listening to 432 Hz music lowered stress measured by salivary cortisol levels, (53). This data shows that a quantum paradigm may explain the effects of gamma frequences on human tissues. Along this line, oscillations can lead to “synchronization”, bringing distant brain areas of in harmony with each other, a phenomenon believed to engender consciousness (54)(55). For example, several sound and light frequences were demonstrated to increase empathy and compassion, suggesting that it promotes the function of the anterior insular cortex (AIC) and anterior cingulate cortex (ACC)(56). In addition, certain oscillatory frequences were found to improve the overall health and wellbeing even in the absence of music, suggesting the beneficial effect of frequency itself rather than the delivering modality. Indeed, another study showed measurable improvement in depression and anxiety scores in college students who utilized a whole-body vibrating platform twice a week (57).

Interoceptive awareness and oscillations

The synchronization of oscillatory brain activity is thought to drive self -awareness, while desynchronization, inhibition of inter-regional CNS signaling, has been demonstrated in general anesthesia, linking intracerebral communication to consciousness (58)(59)(60). Gamma oscillations are believed to connect distant brain regions such as those in charge of movement, memory, and emotion, emphasizing the crucial role of synchronicity (61)(62). Moreover, gamma waves, likely drive interoceptive awareness and cognition, contributing to emotional intelligence, the ability to view one’s actions from another person’s perspective (63)(64). Furthermore, awareness of pain, well-being, or the position of one’s limbs and body parts, comprise interoception or perception of endogenous states. In psychopathology, including SCZ, anosognosia (lack of

insight) is a marker of higher severity of symptoms and frequently a marker of aggressive behaviors (65). For example, somatostatin (SST)-secreting γ -aminobutyric acid (GABA) neurons are depleted in SCZ, likely reflecting poor insight (anosognosia) (66). Along this line, loss of gamma oscillations was also documented in AD and PD, linking poor insight to the depletion of these interneurons (67) (68)(Fig. 3).

EEG desynchronization and violent crime

Several EEG studies on death row inmates with history of violent crime found diminished or absent gamma frequencies, probably highlighting impaired insight (69). Low electrophysiological activity in the right prefrontal cortex and increased striatal activity in these individuals likely mirror anosognosia, a previously described marker of violent crime (70)(71). Indeed, altered prefrontal coherence, especially hypo-frontality, is believed to reflect dysfunctional information processing and inability to distinguish reality from imaginary content , a characteristic trait of poor insight (72).

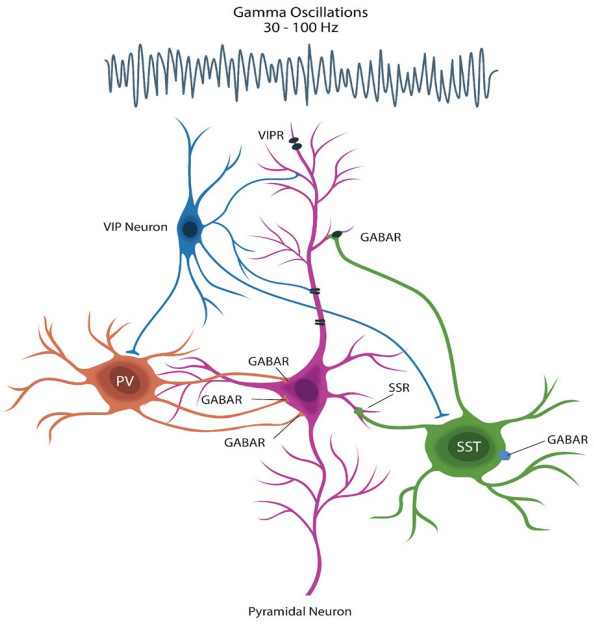

Figure 3. Gamma oscillations comprise a rapid brain rhythm believed to be generated by the synaptic "chatter" of inhibitory GABAergic interneurons, such as somatostatin (SST)-expressing cells which signal with the GABA receptors on other neurons. Loss of inhibitory interneurons disinhibits pyramidal cells, leading to psychosis. Vaso-intestinal peptide (VIP)-releasing neurons counteract this inhibition by inhibiting the inhibitory neurons, an action that leads to the disinhibition of pyramidal cells.

Potential novel interventions

It has been said that the 20th century was an era of biochemistry, when drugs were chosen to address illnesses. In contrast, the 21st century may be a time of biophysical interventions marked by recruiting physical forces, such as oscillations, or electromagnetic energy to influence various molecular pathways in tissues and organs. In addition, the 20th century was a time of specializing and overspecializing in most fields, with emphasis on details, often at the expense of the whole. Conversely, the 21st century appears to highlight healing, restoration, and repair.

MLR and PRT

PRT and MLR aim at restoring the physiological levels of membrane lipids in cell and mitochondrial membranes via natural fats and antioxidants. Altered membrane lipids and oxidation states have been observed in several conditions, including normal aging, SCZ, chronic inflammation, and other neurodegenerative and metabolic disorders.

PRT and MLR can replace and restore functional membrane lipids required for the barrier function. Natural glycerophospholipids, including plasminogen are administered orally to remove and replace toxic lipids and other detrimental hydrophobic molecules, re-storing the physiological permeability of membranes. This was recently demonstrated in vet-

erans with Gulph War Illness (GWI) treated with MLR (65). Likewise, PRT and MLR may have a role in SCZ in which premature molecular senescence appears to be triggered by lipid, especially plasmalogen, peroxidation in cellular and mitochondrial membranes (73). Since plasmalogen disrupts cholesterol biosynthesis, low levels of this lipid in SCZ may explain the cause of dyslipidemia (74). Along this line, a recent study determined the optimal oral dose of PRT as being 900 to 3,600 mg/day over a 4-month period. The authors of this study noted improved cognition and mobility in patients with neurocognitive disorders after about 120 days of PRT in the above doses (75).

PRT, MLR replace damaged membrane lipids in cells via oral intake of natural, unoxidized membrane lipid supplements. MLR has shown efficacy in various conditions involving loss of mitochondrial number and function as well as damage to plasma membranes (43).

PRT and MLR restores the physiological function of plasma membranes throughout the body, including the gut barrier and BBB. This lowers the permeability of epithelial and endothelial barriers, thus averting microbial migration and microbial translocation disorders.

Viruses, including SARS-CoV-2, damage cell membranes as they enter the intra-cellular compartment to replicate. Damaged membranes externalize PS, a universal signal that attracts phagocytes to eliminate infected cells. Cellular senescence upregulates cytosolic iron, predisposing to lipid peroxidation and ferroptosis (76).

Ferroptosis is an iron-induced form of programmed cell death caused by the intracellular accumulation of this biometal in the absence of glutathione peroxidase 4 (GPX4)(77), a lipid repair enzyme. Oxidized lipids have been shown to act as foreign molecules, activating host pattern recognition receptors (PRR), resulting in chronic inflammation, neuropathic pain, depression, and neurodegeneration (78).

Rescue from ferroptosis can be achieved by lowering intracellular iron, increasing GPX4, or replacing the oxidized lipids in cell membranes.

Membrane repair via MLR or PRT reduces neuropathic pain and chronic inflammation, upregulating the number of mitochondria by enhancing organelle dynamics, including fission (17).

Lipid peroxidation and ferroptosis have been associated with several conditions, including myalgic encephalomyelitis /chronic fatigue syndrome (ME/CFS), GWI, chronic pain, and neuropsychiatric disorders. In this regard, ferroptosis-disintegrating cells release proinflammatory alarmins, such as the high mobility group box 1 (HMGB1), known for disrupting the intestinal barrier and BBB (79). Natural membrane supplementation with glycerophospholipids was demonstrated to safely restore the homeostasis of biological barriers, limiting microbial translocation (18). In SCZ, substituting ferroptosis-driving oxidized lipids with healthy glycerophospholipids, may restore the physiological permeability of biological barriers (gut and BBB), averting microbial translocation grom the GI tract into the systemic circulation. Oxidized membrane lipids can also induce toxicity by aberrantly activating AhR, and the downstream GSK3β. Overactive GSK3β has been documented in various neuropsychiatric conditions, especially SCZ and bipolar disorder, as well as in perpetrators of violent crime.

Several antipsychotic drugs, lithium, and the natural compounds berberine and kaempferol, inhibit GSK3β, suggesting that these herbal remedies exert antipsychotic properties, without the adverse effects of conventional psychotropic drugs (Fig.1). In -deed, unlike the antipsychotic drugs that are symptomatic, MLR and PRT may com-prise etiopathogenetic treatments for SMI.

Oscillatory treatment

Oscillations or vibrations are fundamental properties of matter, including the biological systems (80)(81). rom yeast to humans, cells communicate via oscillations, indicating that this is likely a highly conserved mechanism (82)(83)(84). Indeed, it is believed that certain frequencies may be ideal for encoding and transmitting information, suggesting that oscillations may play a role in neurotransmission, functioning in parallel with the synaptic and exocrine/paracrine systems (85)(86).

How brain oscillatory frequencies relate to information processing in neuronal networks is not entirely clear. However, a growing body of evidence has demonstrated that neurons can function as oscillators, making cognition possible by synchronizing with the same frequency oscillators in other brain regions (87)(88). Adaptive resonance theory (ART) and communication through coherence (CTC) are two neurophysiological models which utilize inter-region brain signaling to explain information processing (89)(90). For example, the auditory cortex generates its own spontaneous oscillations in response to the exogenous oscillatory input, synchronizing with the environment (91).

Synchronized oscillations may engender a body-wide communication platform, connecting structures inside and outside the CNS. For example, GI tract microbes en-train “brain-like” oscillations, suggesting that the gut-brain axis may be driven by this modality (92). This is in line with another novel discovery, that oscillations drive the expression of microbial genes, replication, cell cycle progression, and antibiotic resistance (93). Furthermore, the GI tract microbiota oscillations are driven by metabolism, suggesting that the enteric nervous system (ENS) may function as an oscillatory sensor and direct this information to the CNS (94).

Auricular vagal nerve stimmulation (aVNS)

Electrical stimulation of auricular transcutaneous vagal nerve is a modality that can alter the functioning of the neural tissue for therapeutic benefits. Vagus nerve, links the brain directly with several visceral organs, providing a bridge to the GI tract.

Vagus nerve stimulation (VNS) is an invasive procedure which requires implantation of a pulse generator and electrodes close to the cervical vagus. As auricular nerve travels superficially and projects to the nucleus of the solitary tract (NTS) where the vagus nerve also reaches, this method could yield results comparable to those of VNS without being invasiveness (95)(96).

Aside from its central role of increasing norepinephrine, endorphins, and serotonin, VNS was shown to optimize the permeability of gut barrier, averting microbial translocation (97). This is significant as migration of commensal flora (or its components) outside the GI tract is a hallmark of SMI. For this reason, VNS should be used more often as an adjunct to psychiatric treatments.

Gamma band entrainment

Gamma oscillations on EEG have been involved in higher neural functions, including working

memory, attention, and likely consciousness (98). Gamma waves are generated by the GABA interneurons secreting SST, cells that are absent or disrupted in SCZ and MDD (99). Other studies have associated loss of gamma rhythm with aggressive behaviors in forensic psychiatric patients.

The question asked more and more frequently is can we induce gamma waves in a schizophrenic brain to lower psychotic symptoms? Most researchers and clinicians be-lieve that gamma band can be elicited by exposing the patient to this rhythm by various brain stimulatory techniques, including flickering light stimulation (FLS) or exposure to 40 Hz sounds (100).

Pulsed electromagnetic field therapy (PEMF)

Magnetotherapy can be static or pulsed and is produced by the electric current flowing through a coil, generating an electromagnetic field. Exposure to magnets is an old strategy which has been revisited as we learn more about biophysical treatments.

A recent large study, 8-weeks PEMF therapy in patients with treatment-resistant depression emphasized the beneficial role of this modality as an augmentation treatment to pharmacotherapy (101).

PEMF has been used in several conditions, including SMI, chronic pain, wound healing, postoperative pain, and depression (102)(103).

Red light therapy (RLT)

RLT has been used in various pathologies, including SCZ and metabolic disorders in which it was shown to be neuroprotective by improving mitochondrial function, mood, and cognition (104) (105). As higher number of mitochondria can be generated by fission, it has been suggested that fission-inducing modalities could benefit individuals with SCZ (106).

It is believed that RLT lowers inflammation and reduces oxidative stress. In obesity, RLT promotes lipolysis, lowers the adipocyte size, and enhances musculoskeletal system circulation thus, lowering insulin resistance (107).

More studies are needed to clarify the role of RLT in SCZ and dysmetabolism, especially on mitochondrial upregulation.

Other biophysical modalities

Several noninvasive stimulatory techniques, such as low-level laser therapy (LLLT), transcranial alternating current stimulation (tACS) or transcranial magnetic stimulation (TMS), may enhance gamma band synchronization, improving illness in-sight (108)(109)(110). Indeed, a recent study found that 40 Hz auditory steady-state response (ASSR), induced the brain to generate gamma waves, opening novel therapeutic avenues for anosognosia and negative symptoms of SCZ (111).

Aging downregulates SST and upregulates the non-pituitary growth hormone (npGH), lowering gamma band and inducing premature neuronal senescence (112). Since SST-generating GABAergic interneurons are depleted in SCZ, stimulation at 40 Hz may entrain this frequency in the cortex (113).

Conclusion

Both medicated and psychotropic naïve patients with SMI exhibit premature cellular senescence and a higher prevalence of metabolic syndrome, suggesting that both may be inherent components of psychopathology rather than separate entities.

At the cellular level, functional mitochondria likely delay senescence, suggesting that novel therapeutic strategies, addressing this pathology may repair dysfunctional biological barriers.

At the molecular level, aberrant AhR and mAhR activation by the translocated microbes and/or their components, triggers cellular senescence and TJ disruption, contributing to microorganismal migration from the gut lumen into the systemic circulation.

In summary, premature cellular senescence and reduced mitochondrial number may contribute to the pathogenesis of SMI by facilitating microbial translocation. Conversely, early detection of mitochondrial depletion and restoration of organelle number and function by various biophysical modalities may ameliorate neuropsychiatric pathology.

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