

Local Hormones and Neurolipidomics in schizophrenia

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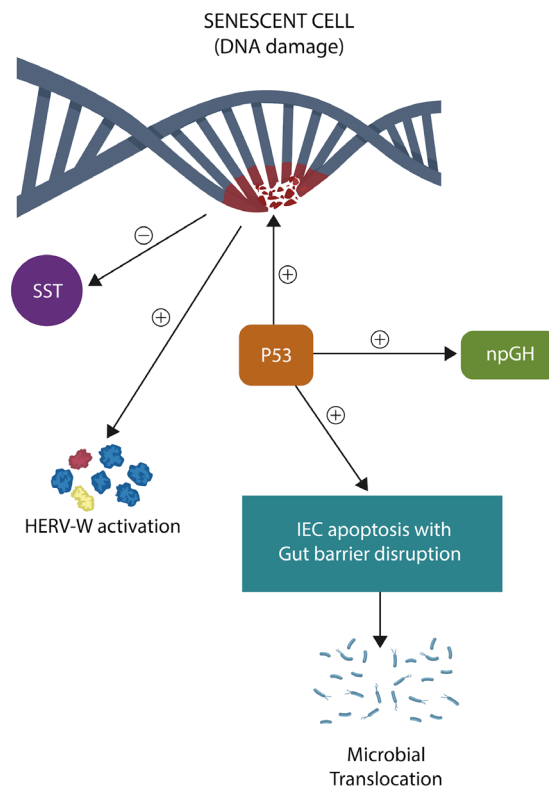
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GRAPHICAL ABSTRACT



- SCZ is associated with genomic damage and premature cellular senescence, affecting both somatic and postmitotic cells.
- Premature neuronal senescence contributes to gray matter loss, involving the neurites and synapses of inhibitory interneurons.
- Loss of somatostatin-expressing GABA interneurons may drive the gray matter loss in schizophrenia.
- Deficient somatostatin upregulates non-pituitary growth hormone, inducing DNA damage and p53-mediated neuronal senescence.

ABSTRACT

Chronic mental illnesses, including schizophrenia, have been associated with premature brain aging manifested on neuroimaging as gray matter loss. This has been associated with impaired insight (anosognosia) and suboptimal treatment outcome. Novel strategies for addressing premature brain aging are urgently needed and somatostatin up regulation may avert gray matter loss. Recent studies, involving non-pituitary growth hormone and p53, have offered early glimpses into the molecular underpinnings of cellular senescence in SCZ. Moreover, age-downregulated somatostatin and activation of Human Endogenous Retroviruses likely drive the negative and cognitive symptoms of SCZ.

In this perspective article, we discuss the following: 1) neuropsychiatric implications of premature brain aging, 2) potential therapies for restoring the homeostasis of somatostatin and non-pituitary growth hormone.

Keywords

Schizophrenia, Neurodevelopmental diseases.

Introduction

Schizophrenia (SCZ) and schizophrenia-like disorders (SLDs) are neurodevelopmental diseases with an average global prevalence of 1%. Antipsychotic drugs, extremely effective for acute psychosis, are much less helpful in the chronic phase, marked primarily by negative and cognitive symptoms [1]. In addition, SCZ outcome studies show that a dismal 13.5% of patients achieve sustained recovery at any time after the first psychotic episode, suggesting that the currently available antipsychotic drugs do not target the central pathology of this illness [2-4].

SCZ neuroimaging studies have consistently reported progressive brain shrinkage, while microscopy found gray matter loss at the expense of dendritic spines and synapses. These findings comprise the proof of concept that the available treatment strategies do not address gray matter loss [5]. Indeed, several studies have found accelerated brain atrophy with some antipsychotic drugs, indicating that maintenance treatment may require different approaches than acute episodes.

Novel studies have emphasized the role of p53, somatostatin (SST), and non-pituitary growth hormone (npGH) in SCZ-associated neuronal senescence [6,7]. In addition, p53 and senescence can activate human endogenous retroviruses (HERVs), ancestral pathogens, residing in the human genome, previously linked to SCZ with negative symptoms [8].

The role of hormones in the etiology of neuropsychiatric disorders is well-established as these conditions often become manifest at puberty or postpartum, life milestones marked by significant stress and “hormonal storms”. In addition, endocrinopathies, including Cushing’s syndrome, hypopituitarism, and primary hyperparathyroidism (PHPT) have been associated with SCZ, emphasizing the intertwinement of endocrinology and neuropathology [9-12]. Moreover, gut microbes, synthesize several hormones, including SST and npGH, likely implicating

the microbiome in SCZ [13-17]. Indeed, commensal flora can synthesize many SCZ-relevant neurotransmitters, including dopamine (DA), serotonin (5HT), norepinephrine (NE), acetylcholine (ACh), melatonin, somatostatin (SST), and oxytocin (OXT), further linking mental illness to various endocrinopathies [18-21].

Numerous studies have connected SCZ with the premature cellular (including neuronal) senescence, emphasizing that DNA damage or defective genomic repair is the likely cause of this pathology [22-24]. It is well-established that SCZ patients live on average 15 to 20 years shorter than their healthy counterparts and develop age-related diseases while still young, highlighting the role of premature aging in this disorder. Indeed, some scholars refer to SCZ as “segmental” progeria, to emphasize this correlation [25].

Gamma oscillations (30-100 Hz) on electroencephalogram (EEG) are altered in SCZ patients, probably reflecting the loss of SST-expressing gamma-aminobutyric acid (GABA) neurons, known for promoting network oscillations [26-29]. Interestingly, both GABA and SST are synthesized by the gut microbes, which are also known for entraining “brain-like” oscillations, linking the microbiome to the EEG waves [30-35]. This is not surprising as in bacteria, oscillations control gene expression, division, cell cycle progression, and antibiotic resistance [35-37].

Do gut microbes communicate with the host via synchronized oscillations? Many believe that certain frequencies may be ideal for low-energy encoding and transmitting information to distant body tissues, suggesting that this platform may be functioning in parallel with the synaptic and exocrine/paracrine neurotransmission [38,39]. Indeed, synchronized oscillations were documented in many tissues, including the endocrine glands, which are known for releasing hormones in regular spurts [40-

43]. At the molecular level, the DNA double helix as well as the p53 genomic repair system, generate spontaneous oscillations, suggesting that macromolecules may engender their own signaling platform - a global molecular network [44]. For example, genome oscillations and gamma waves may generate a quantum code for almost instant information transfer to distant tissues and cells [45,46]. Along this line, desynchronization or uncoupling of a brain region from other areas was demonstrated in general anesthesia or ketamine-induced dissociation states, indicating that awareness requires network synchronization [47,48]. Conversely, noninvasive stimulatory techniques, such as photobiomodulation or transcranial magnetic stimulation (TMS), may avert gray matter loss by optimizing synchronization [49,50]. Indeed, a 40 Hz auditory steady-state response (ASSR) is believed to be an insight biomarker of SCZ, suggesting novel therapeutic avenues for addressing anosognosia and the negative symptoms [51-54]. In addition, SST has been implicated not only in central nervous system (CNS) synchronization but also in brain plasticity, suggests that loss of this hormone may account for the negative and cognitive symptoms of SCZ [55,56]. Indeed, aging downregulates SST and upregulates npGH, linking local hormones to premature neuronal senescence and decreased gamma band [57-59]. Since SST-generating GABAergic interneurons are depleted in SCZ, desynchronization may explain the information processing difficulties [60].

In the GI tract, accumulation of npGH induces intestinal epithelial cells (IECs) senescence via p53 and insulin growth factor-1 (IGF-1), enabling microbes and/or their molecule to migrate into the systemic circulation, eventually reaching the brain [61,6]. Indeed, microbial translocation may be averted by novel approaches, such as lipid replacement therapy (LRT) and or 3-phosphoinositide-dependent protein kinase-1 (PDK1) inhibitors [62].

In this article, we take a closer look at the role of SST and npGH in neuronal senescence, microbial translocation, gray matter loss, and HERV-W activation. We also discuss some potential strategies for restoring the homeostasis of npGH and somatostatin.

Natural Progression of Schizophrenia

The gray matter loss in SCZ, demonstrated in both antipsychotic naïve patients and in those treated with these drugs, suggests that this disorder progresses despite the available therapeutics [63,64]. This is in line with the discouraging SCZ outcome studies, and the continuous need for long-term psychiatric hospitals [65,5].

SCZ starts with a premorbid phase with very few or no symptoms, followed by a prodrome with behavioral changes, but without overt psychosis, which gradually transitions into the psychotic phase marked by acute positive symptoms, multiple hospitalizations, and medication nonadherence. The last phase, beginning in the late 40s or early 50s, is characterized by negative and cognitive symptoms, significant disability and poor response to medications [66] (Figure 1).

Antipsychotics: Electron Donors or Receivers?

Several studies have found that psychotropic drugs which give away electrons do not deplete the CNS gray matter, while electron accepting therapeutics do, suggesting that biophysical properties of these drugs may be more important for the treatment outcome than their receptor affinity or agonist/antagonist status [67,68]. This quantum conceptualization of antipsychotics opens a new research vista - the development of electron donor drugs. For example, dopamine agonists and dopamine (DA) itself are electron donors, while most, but not all, antipsychotic drugs are electron acceptors, suggesting that partial DA antagonists may be preferable for SCZ maintenance treatment [69]. This is significant as electron donors, DA and DA agonists were shown to promote gamma oscillations, while antagonists had the opposite effect [70]. This raises the question of the “anionic brain”: do externalized anionic phospholipids such as phosphatidylserine (PS), a marker of cellular senescence, contribute to the loss of gray matter? It has been established that PS on the cytoplasmic side of cell membranes binds several kinases, containing the pleckstrin homology (PH) domain. This molecular leitmotif regulates cell membrane-recruited kinases, including PDK1, implicated in SCZ [71]. Since PS is externalized in senescent cells, bringing about the “anionic brain”, downstream PDK1-mediated phosphorylation is disrupted, likely disinhibiting glycogen synthase kinase 3 beta (GSK3 β), a SCZ-associated enzyme (see below in Natural and synthetic PDK1 inhibitors). For this reason, LRT may stabilize the function of cell membranes, restoring the homeostasis of these kinases.

We construe, that SST downregulation and the subsequent surge in npGH contribute to premature neuronal senescence and the negative and cognitive symptoms of SCZ. This model is supported by the postmortem mRNA studies, demonstrating low SST and NMDA in patients with negative symptoms [72]. In addition, preclinical studies, have shown that knockdown of parvalbumin (PV) or SST neurons, resembles negative symptoms of SCZ [73].

Premature Senescence and Somatostatin Loss

The most consistent neuroimaging findings in SCZ, gray matter loss and enlargement of lateral ventricles, indicate that reversing this pathology could ameliorate the negative and cognitive symptoms, likely improving the outcome [74-76].

For example, in SCZ, reduced gamma oscillations due to the loss of gray matter volume may be a measurable marker of negative symptoms. At the molecular level, npGH-mediated DNA damage and p53-induced cellular senescence likely drive the gray matter loss [22]. In this regard, recent studies have shown that the interplay between npGH and p53 contributes to the accumulation of damaged DNA and premature senescence (77). Excessive genomic damage downregulates SST, increasing npGH, which in return, promotes brain aging and senescence-mediated pathology [72,78]. Moreover, p53 upregulation activates HERVs, viral fossils previously connected to SCZ [79].

Natural Progression of Schizophrenia

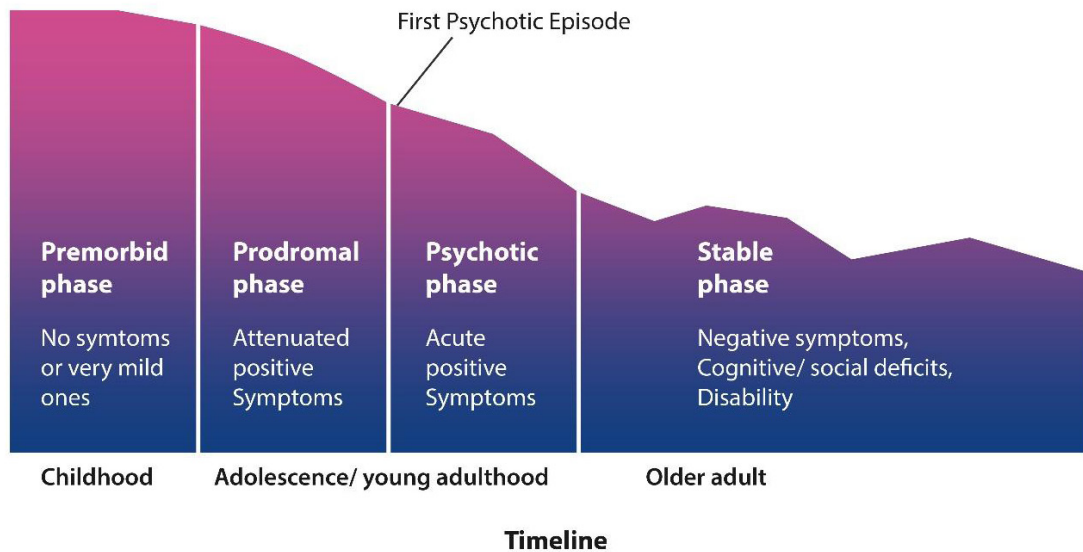


Figure 1: SCZ is believed to be a neurodevelopmental disorder, which starts “in utero”. There are usually no symptoms, or very few symptoms in the initial, premorbid phase. The following prodromal phase is marked by behavioral changes but no overt psychosis. The subsequent psychotic phase is characterized by acute positive symptoms, multiple hospitalizations, and medication nonadherence. The last SCZ phase, beginning around the age of 50, is characterized by negative and cognitive symptoms, significant disability, and poor response to medications. As patients get older, cognitive disorders usually begin during this phase.

Under physiological circumstances, SST augments NMDA, while in SCZ, NMDA is hypofunctional, probably reflecting neuronal senescence and loss of this hormone [80]. Therefore, SST augmentation may comprise a strategy for developing etiopathogenetic treatments for the negative and cognitive symptoms of SCZ [72]. Indeed, In neuronal membranes, SST enhances protein kinase B (also called AKT), inhibiting GSK3 β , an enzyme suppressed by lithium and several antipsychotic drugs. In addition, SST, activates phosphoinositide 3-kinases (PI3K)/AKT pathway, further suppressing GSK3 β [81]. Moreover, AKT upregulation can be accomplished by lowering the neuronal membrane ceramide, highlighting the key role of membrane lipidome in SCZ (see below in Lipid rafts: hubs of cellular senescence).

In IECs, the complex interaction between IGF-1, p53, and npGH, induces premature cellular senescence, disrupting the gut barrier. This facilitates microbial translocation from the GI tract into the host circulation, ultimately reaching the CNS. For example, upon brain entry, microbial LPS was shown to induce neuroinflammation and premature aging, a pathology observed in AD. Indeed, gut microbiota LPS was found postmortem in the brains of AD patients, confirming translocation [82]. Others found, specific microbiota and immunoglobulins in patients with SCZ with negative symptoms, further linking this pathology to microbial migration outside the GI tract [83]. Interestingly, gut microbes, *Bacillus subtilis* and *Escherichia coli* can synthesize SST, demonstrating a possible feedback mechanism of counteracting excessive npGH [84,85].

It is believed that gray matter loss in SCZ occurs at the expense of neurites and synapses of the inhibitory parvalbumin (PV)-expressing GABAergic interneurons, a subgroup of which release SST. It is noteworthy that neurons secreting vasoactive intestinal polypeptide (VIP) inhibit SST and GABA, disinhibiting the pyramidal cells [86,87] (Figure 3). For this reason, VIP inhibitors should be assessed for negative and cognitive symptoms of SCZ.

During the development and childhood, inhibitory GABAergic interneurons are underdeveloped and appear gradually during adolescence and early adulthood. In contrast, the number of excitatory synapses decreases during this time as the CNS undergoes adolescence-mediated recalibration [5,88]. The loss of gray matter volume and gamma oscillations in SCZ and AD is believed to be the result of excessive microglial “pruning” of neurites and synapses [73,89-91]. However, senescence-depleted SST may lead to the loss of dendritic arborizations, producing the same pathological effect as over-pruning [92].

Cellular senescence is an anticancer program marked by resistance to apoptosis, irreversible proliferation arrest, active metabolism, and a specific secretome, known as the senescence-associated secretory phenotype (SASP) which contains enzymes, cytokines, and npGH [6]. These molecules spread the senescent phenotype to the neighboring healthy cells, promoting inflammation. Upregulated npGH may be the cause of senescent cells’ resistance to apoptosis as well as the neuronal reattempts at mitosis. Augmenting gamma oscillatory band may improve insight in

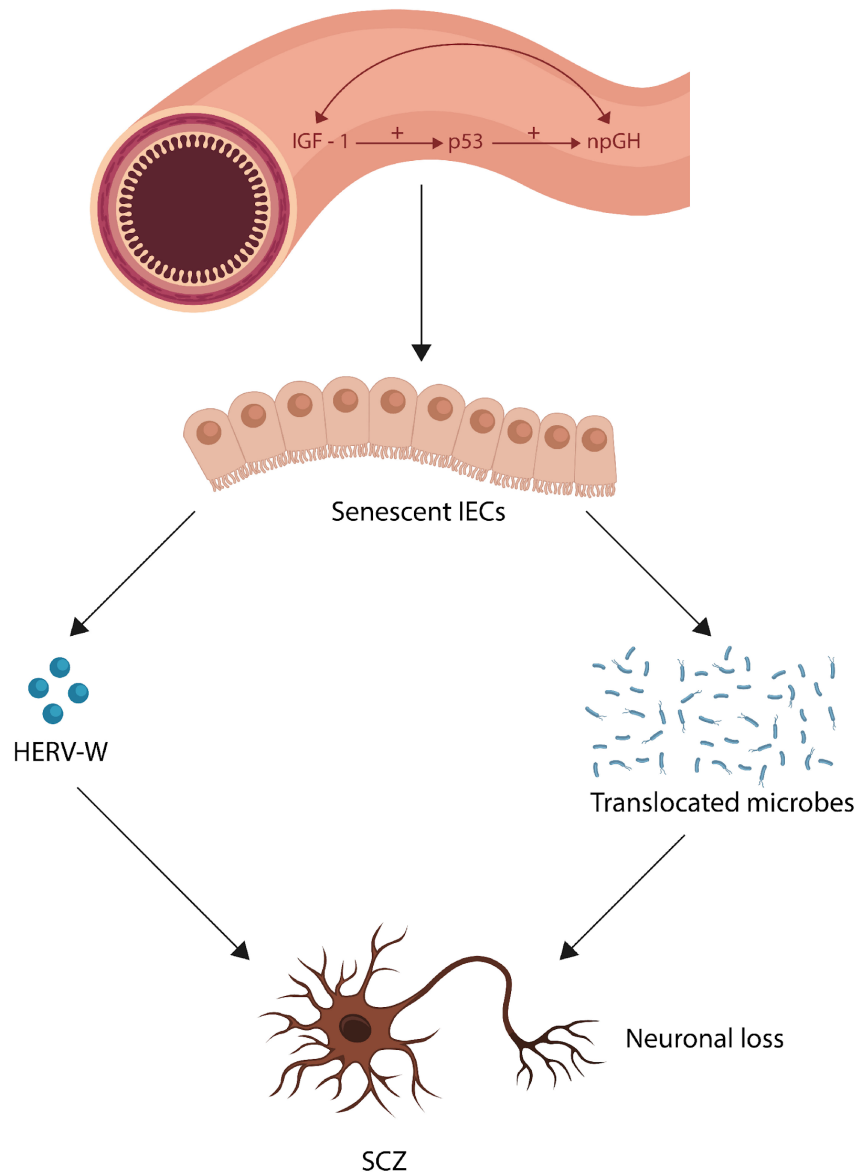


Figure 2: Cellular senescence, an anticancer program, is activated by damaged DNA. The genome guardian, p53 initiates the senescence phenotype and repairs the genome. Senescence lowers SST and increases the levels of npGH which also upregulates IGF-1. In the GI tract, senescent intestinal epithelial cell (IECs) can disrupt the permeability of gut barrier, enabling microbial migration across the lamina propria. Premature neuronal senescence also activates HERVs, viral fossils comprising 8% of the human genome. Translocated bacteria and their molecules can reach the brain, causing neuronal damage by activating microglia.

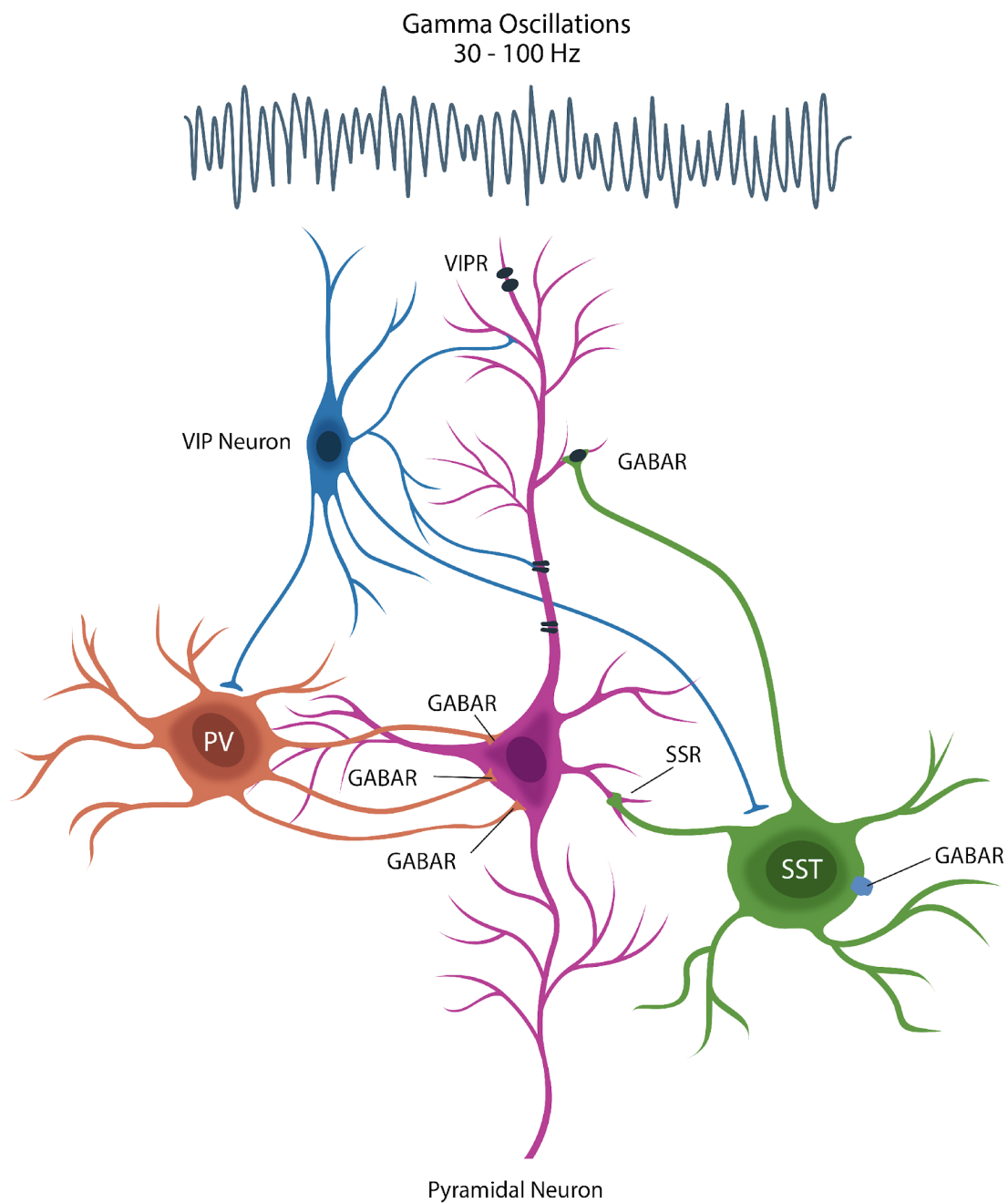


Figure 3: Gamma oscillations comprise a rapid rhythm believed to be generated by the synaptic “chatter” of inhibitory GABAergic interneurons, such as PV-expressing and somatostatin (SST)-expressing cells which interact with GABA receptors. When inhibitory neurons fail to suppress the pyramidal cells, the first psychotic episode may become manifest. In the figure, a VIP neuron inhibits PV and SST cells, disinhibiting the pyramidal neuron.

patients with SCZ, likely by promoting neurite growth, opening novel treatment opportunities [93,94]. For example, several studies have found that 40 Hz intranasal photobiomodulation or transcranial magnetic stimulation (TMS) at 40 Hz were beneficial for negative symptoms and cognition in SCZ [95-99]. Aside from gamma oscillations, anosognosia correlates directly with the loss of both gray matter and SST [100-102]. Can gray matter loss be restored? Studies are contradictory in this area and much more research is needed.

The Good Vibes and The Bad Vibes

Oscillations or vibrations are fundamental properties of all matter, including the living organisms [103,104]. For example, auditory cortex not only responds to the exogenous oscillatory input but also generates its own spontaneous oscillations, likely utilizing these waves as a signaling platform [105]. In addition, pancreatic β -cells utilize electrical and metabolic oscillations to signal with other cells, suggesting that this communication tool is used routinely for intercellular crosstalk [106]. In the CNS, astrocytes communicate via calcium (Ca^{2+}) waves evoked by the GH-activated NMDA channels, implicating this hormone in glial homeostasis [107,108]. This is significant as SCZ, marked by impoverished gamma spectrum, has also been associated with abnormal Ca^{2+} signaling, further implicating SST in this pathology [109]. Simple organisms, including yeast, were shown to communicate with their counterparts via partially synchronized glycolytic oscillations, indicating that this mechanism is highly conserved in nature [110,111]. Moreover, microbial community in the GI tract was demonstrated to oscillate in synchrony with the metabolism, suggesting that the enteric nervous system (ENS) may sense these signals and relays them to the CNS [104].

Oscillation synchronization via “traveling waves”, can transfer information to distant brain regions, likely driving human awareness. In contrast, desynchronization, observed during general anesthesia, induces unconsciousness, emphasizing the role of this signaling platform for the higher order of brain functions [112,113]. Indeed, it is believed that gamma waves, drive both the interoceptive awareness and cognition, contributing to a highly specialized form of information processing [114,115]. Interoceptive awareness refers the individual’s ability to direct attention to the endogenous sensory information, discerning visceral cues on well-being, pain, discomfort, or ownership of limbs and body parts. In SCZ, anosognosia was associated with more frequent decompensations, worse psychotic or negative symptoms, and aggressive behavior, emphasizing the importance of insight for the outcome of this illness neuropsychiatric disorders, including SCZ, are often associated with anosognosia, neglect, or unawareness of the illness presence. For example, strokes of the right hemisphere can cause left-sided neglect with denial of left extremities [118]. Another example of anosognosia is failure to acknowledge one’s own memory impairment, a phenomenon observed in cognitive disorders as well as in viral infections, including HIV and COVID-19 [119,120]. These findings have rekindled the interest of researchers and clinicians in the mental

illness-associated anosognosia. Several neuroimaging studies have linked interoceptive awareness to insight as well as the abundance of GABAergic interneurons in the insular cortex (IC), a brain area associated with insight.

GABAergic interneurons are comprised of PV—expressing neurons, SST-expressing cells and 5-hydroxytryptamine (5HTRs) cells which include VIP-generating neurons (Figure 4). Interestingly, SST interneurons and some VIP neurons express muscarinic receptors, which are currently targeted in SCZ [121]. For example, xanomeline, a muscarinic M1/M4 agonist, exerts antipsychotic properties despite very low affinity for DA receptors, suggesting that non-dopaminergic transmission may be implicated in SCZ [122]. Therefore, enhancing GABAergic signaling to ameliorate anosognosia could likely be accomplished by inhibiting VIP-expressing GABAergic interneurons (Figure 4) [123]. Ameliorating anosognosia may significantly improve the long-term prognosis of SCZ, therefore, searching for therapeutics in this area is of paramount importance [124]. Along this line, a recent preclinical study has identified SST interneurons in anterior insula, suggesting that depletion of this hormone may impair insight by driving neuronal senescence [125].

Taken together, SCZ characteristics, including decreased gray matter volume, anosognosia, and impaired gamma oscillations may mirror the loss of inhibitory SST interneurons. Absent SST, npGH is upregulated, leading to cellular senescence and likely, the negative symptoms of SCZ [126,127].

HERVs, Ancient Viruses Causing Contemporary Illness

DNA damage-associated cellular senescence was shown to activate HERV-W, an ancient retroviral element, associated with SCZ [128-133]. HERV-W is encoded in the regulatory region of GABA receptor B1 (GABBR1), linking these pathogens to the inhibitory interneurons. HERV-W encodes for syncytin-1, a placental protein known for fusing individual trophoblasts into the syncytiotrophoblast, enabling placentation. Excessive syncytin-1 may trigger pathology by fusing healthy neurons, a phenomenon observed in neurodegenerative disorders as well as in normal aging [134-136]. Most HERVs are incomplete genes, which are never transcribed, however, some of these elements were “domesticated” in time and had assumed physiological functions. Several studies have shown that HERVs can lay dormant in host DNA until activated by infections, cellular senescence, or placental hormones [137,138]. Upregulated by the damaged DNA, npGH induces cellular senescence and disseminates this phenotype via SASP. Damaged DNA upregulates p53, which in turn, induces further npGH transcription [6]. Recent studies have revealed that p53 can activate HERVs, utilizing them as tools against various cancers, suggesting that these dormant pathogens may destabilize the genome [139-141]. Elevated HERV-W levels were previously documented in SCZ, linking these viral relics to the genetics of SCZ [142].

In our previous work, we have discussed SARS-CoV-2 inhibition

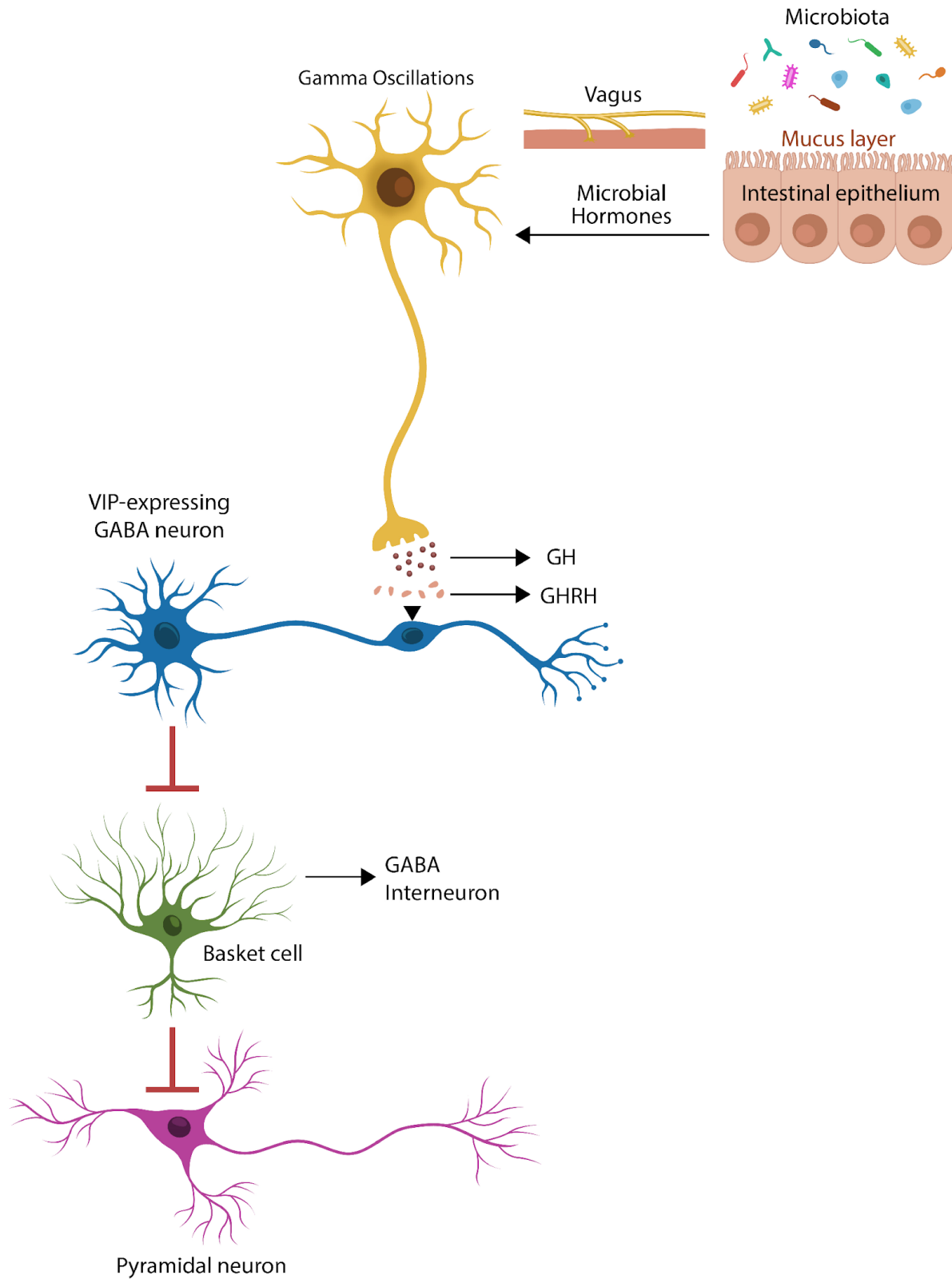


Figure 4: The ENS gastrin neurons sense microbial input from the gut lumen and relay these signals to the CNS via vagal, humoral, and oscillatory pathway. Gastrin neurons secrete GH to activate the VIP-expressing GABA cells. These cells inhibit (the inhibitory) GABA and SST neurons, releasing the pyramidal cells' inhibitory brakes.

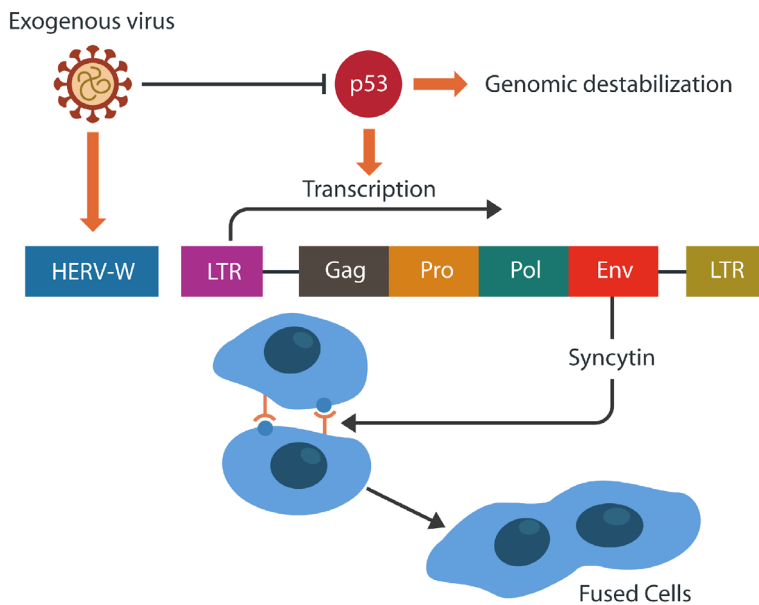


Figure 5: Contemporary viruses, including COVID-19, activate HERV-W gene, while inhibiting p53. Both actions allow for the transcription of HERV envelope (ENV) gene, producing excessive syncytin-1. This protein drives pathological cell-cell fusion in various organs, including the brain. Fusion of postmitotic neurons may predispose to the development of cognitive or negative symptoms of SCZ.

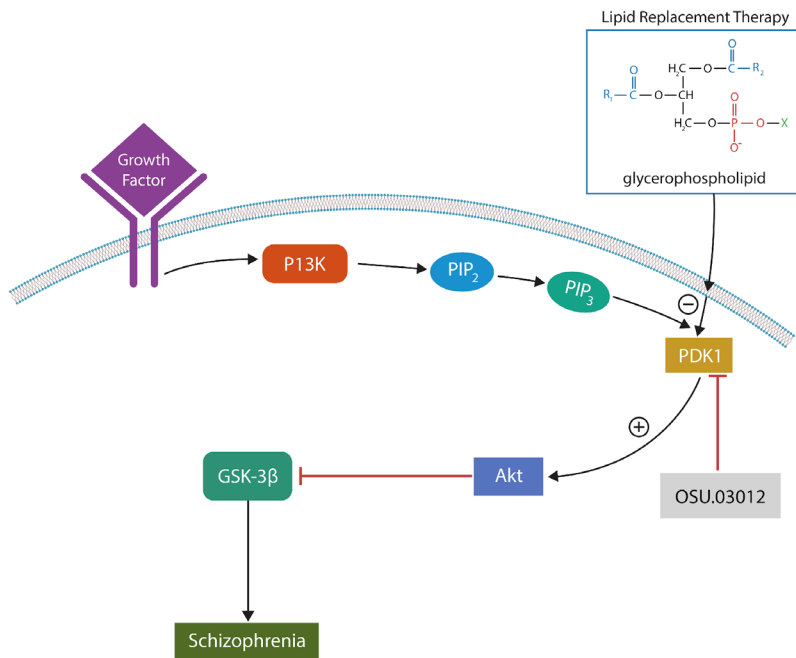


Figure 6: LRT exerts neuroprotective action in SCZ via PDK1/AKT/ GSK3β axis. PS (part of glycerophospholipids) binds PDK1, recruiting this kinase to the cell membrane. Natural or synthetic PDK1 inhibitors, enhance AKT-blockade of GSK3β, ameliorating the negative symptoms of SCZ.

of p53 and HERV-W activation, pathological cell-cell fusion and virus-induced neurocognitive deficits [143] (Figure 5). For this reason, we will not discuss HERVs in more detail here. Taken together, contemporary viruses can activate HERVs to enhance their own infection. Neurocognitive deficits, autoimmune disorders and SCZ were associated with reactivated HERVs.

Novel, Natural Antipsychotic Strategies for Schizophrenia

Membrane and serum lipids are altered in SCZ, suggesting that a better understanding of neurolipidomics, could lead to the development of novel therapies for negative and cognitive symptoms [144]. These include natural lipids with plant-derived PDK1 inhibitors, aiming at replacing the oxidized membrane lipidome with natural phospholipids.

Lipid replacement Therapy (LRT) adapted for schizophrenia (LRT+K)

LRT refers to the oral intake of natural glycerophospholipids to which we added kaempferol (3,4',5,7-tetrahydroxyflavone), a natural flavonoid. The aim of LRT+K is to gradually replace damaged lipids in neuronal cell membranes with natural glycerides, containing phosphatidylserine (PS) and plant-derived kaempferol.

LRT interacts with a pathway previously implicated in SCZ: PDK1/ AKT/GSK3β (3-phosphoinositide-dependent kinase 1/ protein kinase B/ glycogen synthase kinase 3). PDK1, found upstream of AKT and GSK3β, contains a pleckstrin homology (PH) domain, which binds PS in the cytoplasmic leaflet of cell membranes. PS/PDK1 attachment has two beneficial effects: 1) recruitment of PDK1 at the cell membrane, and 2) maintaining PDK1 in inactive conformation (Figure 6) [145,146]. This modulates the downstream phosphorylome, inhibiting, GSK3β. Uninhibited GSK3β promotes psychosis and several antipsychotic drugs and lithium are inhibitors of this enzyme [147].

AKT also contains a PH domain which binds PS in the lipid rafts. However, unlike PDK1, upon attachment to PS, AKT becomes active (probably via autophosphorylation). Activated AKT suppresses the downstream GSK3β, lowering the risk of psychosis (Figure 6) [145,146]. In contrast, kaempferol inhibits PDK1 (by a non-PH mechanism), probably via regulating the phosphorylation of AKT and GSK3β. Therefore, unlike antipsychotics and lithium, kaempferol, blocks PDK1 in a totally natural manner [148]. In addition, OSU-03012, a synthetic PDK1 inhibitor, is currently being evaluated for anticancer efficacy. OSU-03012 may help LRT by inactivating PDK1 by a mechanism different than PS (Figure 6). Taken together, PS, a component of LRT, inactivates PDK1 by recruiting it to the cell membrane. Conversely, PS attachment, activates AKT effectively suppressing GSK3β and psychosis.

Lipid Rafts: Hubs of Cellular Senescence

Lipids play a key role in the pathogenesis of negative and cognitive symptoms of SCZ not only because of lipid oxidation but also because of decreased membrane cholesterol [149]. For example, a study found that external radiofrequencies-induced cell membrane

oscillations depend on the lipid composition (the more cholesterol, the more fluid the membrane) [150]. Cholesterol modulates the bilayer structure of cell membrane by altering not only the fluidity, but also the thickness, compressibility, exocytosis of secretory vesicles, and oscillatory activity. Suggesting that in the absence of this lipid, cell membrane vibrations are attenuated [151]. In this regard, ceramide has a more rigid molecular structure and restrains the oscillatory activity [152].

In senescent neurons, lipid rafts contain a disproportionate amount of ceramide compared to cholesterol, suggesting that old membranes are much less flexible and resistant to synchronization [153,154]. Indeed, earlier studies have implicated ceramide and sphingosine-1-phosphate in SCZ, further linking neuronal senescence to the biophysical properties of cell membranes [155-158]. Interestingly, several antipsychotic drugs intercalate themselves in the lipid bilayer, altering the biophysical properties of cell membranes. This suggests that antipsychotics may exert their actions by dopaminergic and non-dopaminergic mechanisms, the latter, including biophysical [159]. For example, cell membrane sterols were found altered in individuals at ultra-high risk of psychosis (UHR), suggesting that the membrane lipidome may be crucial for the pathogenesis of SCZ [160]. Likewise, in older individuals, the lipid composition of neuronal plasma membrane is altered in favor of ceramide, as cholesterol is replaced with this lipid in older individuals [161-163]. Indeed, loss of cholesterol may reduce gamma frequencies, predisposing to cognitive deficit [164]. Moreover, npGH was demonstrated to upregulate cell membrane ceramides, suggesting that aside from the genome, this hormone may also damage the cell membranes [165]. Taken together, as LRT provides healthy natural lipids to neuronal lipid rafts, this intervention may rehabilitate not only the lipidome but also the gray matter and the oscillatory gamma activity.

Natural and synthetic PDK1 inhibitors

Protein kinases are enzymes that transfer phosphate groups from adenine triphosphate (ATP) to specific proteins. PDK1 inhibitors exert their beneficial effects by inhibiting GSK3β. Natural PDK1 inhibitors are ubiquitous, being present in numerous fruits and vegetables and for this reason, have no known adverse effects (Table 1).

Table 1: Natural flavonoids PDK1 inhibitors.

PDK1 inhibitor	Plant	References
Kaempferol	fruits, vegetables, and herbs	166
Quercetin	Onions, kale, broccoli	167
Myricetin	Oranges, berries, tomatoes, nuts, tea	168
Epigallocatechin-3 gallate	Green tea	169
Lupiwighteone isoflavone	Glycyrrhiza glabra; Lotus pedunculatus	170
Delphinidin	Citrus fruits	171
Honokiol	Cherries, berries, grapes	172
Delphinidin	Cranberries, Concord grapes, Pomegranates	173

Synthetic PDK1 inhibitors

Several synthetic PDK1 inhibitors have been developed, but few can cross the BBB. The exception is OSU-03012, a celecoxib derivative without cyclooxygenase-2 inhibitory activity, which exerts antiviral properties and is currently being evaluated for glioblastoma (Figure 6) [174,175]. OSU-03012 may be a suitable candidate for SCZ with negative and cognitive symptoms. At present, several other PDK1 inhibitors are in clinical trials for in AD.

Conclusions

For the past 70 years, psychiatry has been obsessed with the postsynaptic dopaminergic blockade and paid much less attention to the gray matter loss, enlargement of lateral ventricles, and the paucity of gamma oscillations. Novel SCZ studies have started to emphasize the importance of local hormones, GABAergic interneurons, as well as the lipid composition of neuronal membranes. The therapeutic strategies derived from these models may, for the first time, improve SCZ outcomes. Limiting gray matter loss, restoring the homeostasis of SST interneurons, and npGH inhibition, may address the root cause of SCZ. Biophysical approaches, including TMS or photobiomodulation at 40 Hz, may promote healthy oscillatory activities, restoring the integrity of the connectome and the synchronization of brain areas. Acknowledging brain oscillations as a unique communication platform has the advantage of influencing the connectome in a noninvasive manner. Together, these approaches may address the etiopathogenesis, rather than SCZ symptoms, bringing for the first time, remission instead of symptom reduction.

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