Review

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Love in the Time of COVID: Psychiatric Lessons from Oxytocin and the “Endocrine Organ”

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Abstract: Oxytocin, known as the "love hormone," is poduced in the posterior hypothalamus and participates in numerous physiological processes, including social intelligence, sexual activity, and metabolism. SARS-CoV-2 virus, the etiologic agent of the COVID-19 pandemic, has been shown to suppress oxytocin release from the intestinal epithelial cells, resulting in microbial migration outside of the gut lumen. *Limosilactobacillus reuterii,* a commensal known for producing oxytocin, normalizes the gut barrier function and exerts antiviral properties, including against the SARS-CoV-2 virus. This may explain the beneficial effect of oxytocin in schizophrenia, a condition associated with a dysfunctional gut barrier and microbial translocation from the gastrointestinal tract into the systemic circulation. The molecular underpinnings of oxytocin in the central nervous system are not entirely clear. However, as viruses target tight junctions, the molecular Velcro that holds the barrier cells together, oxytocin enhances the barrier function. In this mini-view, we summarize what is known about the role of oxytocin in schizophrenia and discuss natural and synthetic compounds that could optimize gut barrier permeability.

Keywords: schizophrenia; microbiome; endocrine organ; virus; autoantibodies

Introduction

The COVID-19 pandemic was an eye-opener for many medical disciplines. It highlighted viral exploitation of the physiological cellular ingress routes (endocytosis), generally utilized for signaling, receptor recycling, engulfment of xenobiotics, and cell-cell adhesion. These entry pathways play an essential role in cancer, neurodegenerative disorders, and schizophrenia (SCZ).

Viruses like SARS-CoV-2 exploit other cellular products, including hormones and neurotransmitters. For example, the Japanese Encephalitis Virus (JEV) usurps dopamine (DA) receptors to enter cells, therefore disrupting dopaminergic signaling (1). Moreover, viruses can hijack cellular senescence, an antitumor program in which the cell permanently exits the cell cycle to deter malignant transformation.

Due to its antiviral properties, oxytocin (OXT) is targeted by the SARS-CoV-2 virus, resulting in decreased signaling with OXYTOCIN receptors (OXRs), which affects among other things, male and female fertility (2)(3)(4). Indeed, patients with SCZ have fewer offspring than the general population, which may, at least partially, result from dysfunctional OXYTOCIN signaling (5). This may be further substantiated by the COVID-19-related drop in birth rate in many countries, including the US (6)(7).

The connection between viruses and SCZ has been documented for several decades. For example, women pregnant during the US rubella epidemic in 1964 gave birth to offspring that developed autism spectrum disorders (ASDs) or SCZ more often than the population at large, suggesting that many viruses, probably including COVID-19, may contribute to these sequelae (8).

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Other studies found that dormant viruses, such as human endogenous retroviruses (HERVs), could promote SCZ (9). Moreover, molecular mimicry between the M2 protein of influenza A virus and N-methyl-D-aspartate receptors (NMDARs) can explain the "autoantibodies" against this protein found in some SCZ patients, further linking viruses to chronic psychosis (10)(11). These "autoantibodies" are likely conventional immunoglobulins directed at the M2 viral protein. Moreover, some gut microbes, including *Helicobacter pylori*, express NMDA receptors, further enhancing the fact that translocated microbes can elicit the formation of antibodies against these proteins.

The gut microbes are known to produce all the neurotransmitters and hormones the host generates, so the microbiome is often conceptualized as an endocrine organ (12)(13). *Limosilactobacillus reuteri* (*L. reuteri*), one of the OXYTOCIN-producing gut microbes, has been less abundant in humans over the past two decades, probably accounting for the increased prevalence of autoimmune disorders (14). *L. reuteri is* found in the GI tract, urinary tract, skin, and breast milk, where it exerts anti-inflammatory, antimicrobial, and antianxiety actions and produces vitamin B12 and histamine, contributing to the GI tract's homeostasis (15).

OXYTOCIN is a peptide hormone synthesized in the hypothalamic paraventricular (PVN) and supraoptic (SON) nuclei and stored in the posterior pituitary. Aside from *L. reuteri*, intestinal epithelial cells (IECs) produce OXYTOCIN, especially when exposed to the GI tract hormone secretin (16). This may explain the documented beneficial effect of secretin in refractory SCZ (17). OXYTOCIN signals with OXRs spread throughout the brain and are more numerous in the hypothalamus (18).

To function adequately, OXRs require cholesterol, a lipid that delays receptor degradation. Thus, OXYTOCIN signaling is likely deficient at low cholesterol levels (19). In addition, statins can exhibit extracerebral adverse effects, such as infertility and muscle breakdown (20)(21). Moreover, increasing evidence suggests that the beneficial effects of statins on endothelial cells may be independent of their cholesterol-lowering properties (22).

The prosocial role of OXYTOCIN and the fact that abundant OXYTOCIN receptors are expressed in the insular cortex (IC) and anterior cingulate cortex (ACC) has led many researchers and clinicians to see a functional similarity between OXYTOCIN and von Economo neurons (VENs), the large bipolar cells that project to a distant area of the brain (23). Indeed, VENs are part of the salience network (SN), a neuronal assembly that shifts attention from exteroception to interoception or from the central executive network (CEN) to the default mode network (DMN), depending on the stimulus relevance (24).

Although not officially included among senolytic or xenomorphic agents, OXYTOCIN meets the criteria for the latter. Senotherapeutics are divided into senolytic compounds that accelerate the elimination of senescent cells and xenomorphics that delete the senescence markers, "rejuvenating" the cell.

This mini-view looks closely at potential interventions based on the microbial translocation hypothesis.

Cellular Senescence

Under physiological circumstances, after replicating 40-60 times, somatic cells undergo senescence, marked by proliferative arrest and a rewired metabolism. Exceptions to this rule are cancer cells and probably stem cells, which can divide indefinitely. For example, HeLa cells, derived from a 1950s cancer patient, are still thriving in labs worldwide and have been used recently for research on the SARS-CoV-2 vaccine (25). Aside from replicative senescence, cells can activate the senescence program when in danger of malignant transformation or damaged DNA needs repair.

Cellular senescence is marked by irreversible replication arrest, resistance to apoptosis, active metabolism, and the release of a toxic secretome known as the senescence-associated secretory phenotype (SASP). The accumulation of senescent cells is believed to contribute to organismal aging, as SASP can spread the senescent phenotype locally and systemically. For example, aging endothelial cells (ECs) release SASP directly into the systemic circulation, disseminating senescence throughout the body (26).

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Several studies have shown that although senescence itself protects against malignant transformation, SASP maintains a degree of low-grade inflammation that may predispose to cancer.

Phagocytes clear senescent cells in a process known as efferocytosis. When efferocytosis is defective, senescent cells accumulate, triggering inflammation (27). In patients with severe mental illness, efferocytosis is defective, leading to premature aging and low-grade inflammatory responses. Indeed, SCZ patients live on average 15-20 years shorter than the general population and develop age-related illnesses earlier in life, leading some researchers to conceptualize SCZ as a "segmental progeria" (28). Along this line, telomeres are shorter in patients with SCZ, and senescent markers, such as p21, p16, and SA-β-galactosidase activity, are frequently elevated.

OXYTOCIN opposes cellular senescence, especially the SASP, and isolation-induced premature aging observed during the pandemic lockdown (29). Along this line, intranasal OXYTOCIN has been shown to improve social interaction and communication in children with ASD, highlighting a novel therapeutical strategy for this condition. Aside from eliciting pro-social behavior, OXYTOCIN exerts direct antiviral effects, especially against the SARS-CoV-2 virus, as reported by several studies (30). Indeed, this action brought OXYTOCIN into the spotlight of research during the COVID-19 pandemic.

In the GI tract, OXYTOCIN receptors are highly represented in the myenteric plexus and are involved in motility, inflammation, and barrier permeability. For example, OXYTOCIN receptors prevent microbial translocation outside of the GI tract, an action canceled by vagotomy, a finding that implicates cholinergic neurotransmission, probably via signal transducer and activator of transcription 3 (STAT3), in OXYTOCIN release (31)(32). In addition, as OXYTOCIN upregulates IL-10, an anti-inflammatory cytokine that shares its receptor with IL-22, it likely upregulates this "guardian of the gut barrier," preventing translocation (33). Moreover, like IL-22, OXYTOCIN mediates wound healing, suggesting that it also improves biological barriers.

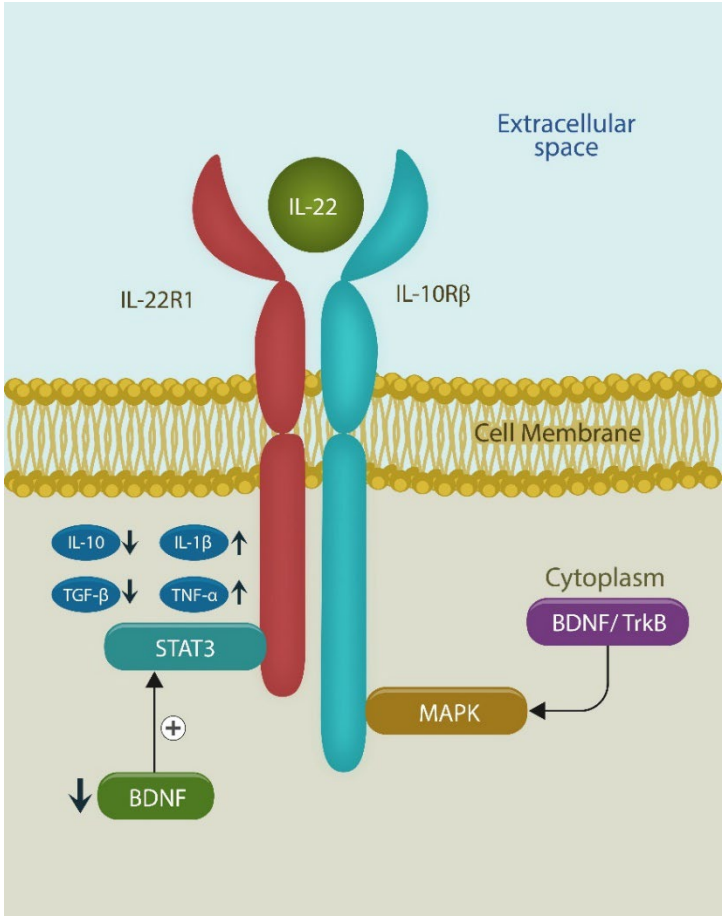

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Figure 1. IL-10 and IL-22 share their receptor (IL-10 receptor beta and IL-22 receptor 1). IL-22 attachment activates both STAT3 and MAPK. Decreased BDNF upregulates STAT3, linked to the cholinergic system and the brain, especially the insular cortex (IC) and anterior cingulate cortex (ACC).

Schizophrenia Outcome Studies

Gray matter volume (GMV) reduction, a hallmark of SCZ demonstrated by many neuroimaging studies, is seldom considered in the etiopathogenesis of this disorder, probably because it is refractory to most of the available treatments. GMV loss is in line with SCZ outcome studies, which show that only a minority of patients reach sustained recovery, suggesting that brain volume atrophy may progress unhindered by the antipsychotic drugs we currently utilize (34). White matter is also depleted in SCZ, although less than the gray matter, and likely reflects the damaged myelin.

GMV reduction in SCZ, associated with aggression and violence, occurs in both medicated and unmedicated SCZ patients, suggesting that aggressive behavior is an inherent part of the disease and not caused by the antipsychotic treatment only (35)(36)(37).

OXYTOCIN treatment may improve SCZ outcomes, as it was shown to preserve gray matter and ameliorate traumatic brain injury (TBI) and epilepsy (38)(39). This may alter the disease course, improving functional recovery.

With current SCZ treatments, 33% of patients relapse during the first 12 months after an initial psychotic episode, 26% remain homeless at two-year follow-up, while five years after the first psychotic outbreak, only 10% are employed (40)(41)(42).

Clinically, the natural progression of SCZ evolves in four stages: an asymptomatic phase followed by a prodrome with mild but not overly psychotic symptoms. Phase III is manifested as frank psychosis and comprises the first psychotic episode and subsequent relapses. In stage IV, usually after midlife, the positive symptoms gradually subside and are replaced by negative and cognitive manifestations (43).

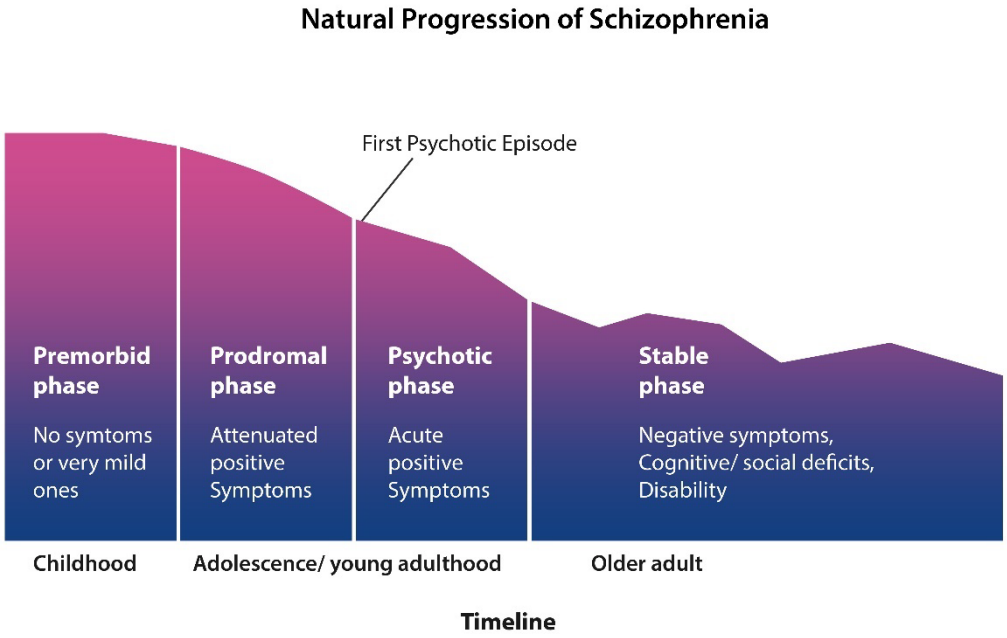

Figure 2. SCZ starts in early childhood with a premorbid phase with no symptoms or mild ones. Attenuated symptoms, such as social isolation, anxiety, and insomnia, mark the prodromal phase. This phase blends gradually into psychosis, during which patients are usually hospitalized many times for exhibiting positive symptoms. Around midlife, the positive symptoms gradually subside and are replaced by negative and cognitive manifestations (figure adapted from Liberman).

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The "Love Hormone" and the Fat

In humans, cholesterol comprises 35% of cell membranes and is found in the cell membrane's lipid bilayer, dispersed among phospholipids. Cholesterol provides stability to cells and organelles by maintaining an optimal balance between membrane fluidity and rigidity (Figure 1). In neurons, cholesterol is a significant driver of dendritic spine and neurite growth, implicating this lipid in memory and cognition (44). In this regard, loss of dendritic arborization in inhibitory interneurons was associated with aggression in patients with SCZ, suggesting that this disorder may be caused by a lipidome dysfunction (45).

Cholesterol is an essential allosteric modulator of OXYTOCIN receptors (OTRs), stabilizing this high-affinity bond. This raises the possibility of statins altering OXYTOCIN signaling, precipitating iatrogenic aggression. Indeed, several studies reported statin-induced violence, suggesting that plasmalogen, the "natural statin," should be used for the management of hypercholesterolemia in psychiatric patients (46)(47).

In a previous study, we hypothesized that low cholesterol and hypovitaminosis D contribute to GMV reduction, a hallmark of SCZ and aggression. We hypothesized further that a subgroup of patients with increased expression of the ATP binding cassette subfamily A member 1 (ABCA1) gene is more vulnerable to cholesterol-lowering strategies (48). Hypovitaminosis D was demonstrated in over 95% of forensic patients with SCZ, implicating this nutrient in neuropathology (49). Low levels of cholesterol, a vitamin D precursor, were associated with both violent behavior and suicide, highlighting further the role of lipidome in this pathology (50)(51)(52).

The brain is the cholesterol-richest organ in the body. In the central nervous system (CNS), cholesterol is a component of the lipid bilayer of neuronal membranes and the myelin sheath. Aggressive and violent behaviors in patients with SCZ are directly correlated with gray matter loss, especially in the right superior frontal cortex, left inferior parietal region, insular cortex (IC), and ventromedial prefrontal cortex (VMPFC)(53)(54)(55). In contrast, suicidal behavior (self-aggression) was associated with white matter loss, implicating defective remyelination in this pathology (56).

Cholesterol depletion was previously demonstrated to disrupt glutamate α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptors, leading to the loss of synapses and dendritic spines, pathologies documented in SCZ variants marked by violent behaviors (57)(58).

Several studies have found that OXYTOCIN can trigger reactive anger and aggression, especially in SCZ patients (59)(60)(61). Indeed, despite promoting prosocial behavior, OXYTOCIN may, in some situations, enhance aggression. However, the relationship with low cholesterol or lipid peroxidation requires more studies. Along this line, several articles have associated SCZ with lipid peroxidation in cells, including the neurons. At the same time, lipophilic antipsychotic drugs, such as phenothiazines, infiltrate the membrane lipid bilayer, repairing the lipids with their antioxidant properties (62)(63). Several new phenothiazines oppose lipid peroxidation, highlighting the dopamine-independent antipsychotic action of these drugs (64). Indeed, novel phenothiazine derivatives with potent antioxidant properties are available to treat heart disease and cancer. To our knowledge, despite the phenothiazine core, these agents were never evaluated for mental illness. For example, tetracyclic and pentacyclic phenothiazine derivatives are potent antioxidants and free radical scavengers capable of repairing the membrane lipids and rescuing cells, including the neurons (65). Phenazines are natural phenothiazines generated by various species of soil and marine microbes and exhibit antibiotic, anticancer, and antipsychotic properties (66).

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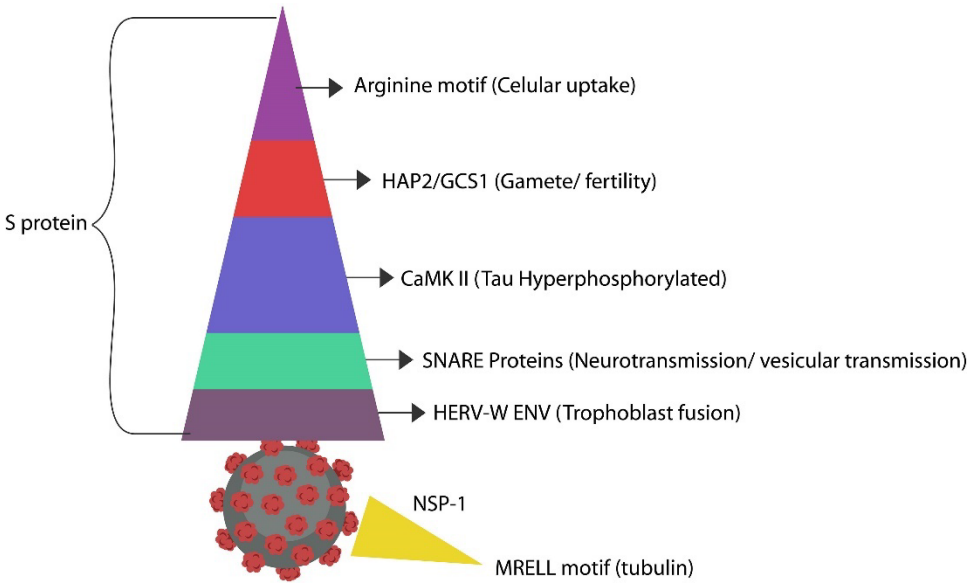

Figure 3. Schematic representation of the SARS-CoV-2 virus antigen S (spike) with the known repeats (motifs) mimicking human proteins. The triple arginine motif promotes pore-forming in cell membrane via its side chain. HAP2, or GCS1, is a family of membrane fusion proteins found in the sperm cells that are directly related to male fertility. Calcium calmodulin kinase II hijacks OXYTOCIN and promotes phosphorylation of Tau protein (found in both the brain and placenta). SNARE proteins participate in vesicular and synaptic transmission. Human endogenous retrovirus (envelope) sequences mimic placental syncytin, a trophoblast fusogen. NSP-1 is a non-S antigen of SARS-CoV-2 protein that resembles tubulin found in the CNS and placenta.

Aryl Hydrocarbon Receptor, the New Kid on the Block

The aryl hydrocarbon receptor (AhR) was initially known as the dioxin receptor. However, many ligands at this protein have been identified over the years, some of which are relevant to neuropathology. For example, serotonin (5-HT), melatonin, and dopamine (DA) are upstream AhR ligands, bringing this protein into the psychiatric arena. In addition, AhR is the master regulator of cellular senescence because it can sense endogenous and exogenous metabolites, xenobiotics, and toxicants, inducing premature molecular aging to lower the risk of malignant transformation.

AhR negatively regulates lactate and its posttranslational modification, lactylation. Consequently, dysfunctional AhR may drive both premature neuronal and glial aging, as well as the excessive lactylation documented in SCZ and other psychotic disorders (67). For example, senescent microglia with excessive histone 3 (H3K18) lactylation were demonstrated to adopt a neurotoxic phenotype, eliminating healthy synapses and neurons, as documented in SCZ and AD (68).

Translocated microbes trigger iron sequestration in host macrophages, a phenomenon known as nutritional immunity. Nutritional immunity aims to withhold iron from the invading pathogens, decreasing infectivity (69). However, low circulatory iron often causes bacteria in host tissues, including the brain, to adopt a dormant phenotype (70). For example, dormant brain microbes were documented in Alzheimer's disease (AD), while a virome (viral microbiome) was recently identified in the SCZ brains (Broadman area 46) (71)(72). The dormant microbes can be reactivated when iron becomes available, causing neuropathology. Moreover, iron regulatory proteins, such as hepcidin, are AhR ligands, emphasizing a previously unknown relationship between AhR and nutritional immunity (73).

AhR is located at the biological barriers and comes readily into contact with endogenous and exogenous nutrients and toxins that bind this receptor with various affinities, eliciting different degrees of activation. Excessive AhR activation likely disrupts the TJ molecules, opening paracellular pathways used by microbes or their components to migrate outside the lamina propria (74). In this regard, SCZ with negative symptoms was associated with antibodies against translocated *Hafnei alvei,*

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Pseudomonas aeruginosa, Pseudomonas putida, and Klebsiella pneumonia, which are proof of concept of microbial migration in SCZ.

Viruses also induce cellular senescence by manipulating AhR through their antigens. For example, the SARS-CoV-2 virus usurps OXYTOCIN via OXYTOCIN-activating motifs such as calcium calmodulin kinase II (CaMKII). At the molecular level, OXYTOCIN accumulates and phosphorylates CaMKII, lowering the circulatory levels of this hormone. Moreover, the S antigen of the SARS-CoV-2 virus contains soluble N-ethylmaleimide-sensitive fusion protein attachment protein receptors (SNARE) repeats that can interfere with the vesicular release of OXYTOCIN, further lowering the systemic level of this hormone (75) (Figure 3).

Molecular imitation of placental proteins by viral arginine repeats, HAP2, tubulin, tau, and human endogenous retroviruses (HERVs) facilitates both the infection and the development of antibodies against host proteins.

Taken together, molecular mimicry of reproductive proteins leads to reduced birth rates as documented worldwide. Viral repeats (motifs) are known AhR activators, an action that manipulates this protein into a pro-viral role. Active AhR lowers interferon-gamma, a potent antiviral defense (76)(77). Therefore, AhR inhibitors exert not only anti-translocation but also antiviral properties.

Potential Interventions

The microbial translocation hypothesis opens new therapeutic strategies beyond dopamine and the synapse. These strategies include senotherapeutics, barrier enhancers, and AhR inhibitors.

Senotherapeutics

SCZ has been associated with premature molecular aging, which is reflected in decreased longevity by 15-20 years compared to the general population. Premature molecular aging likely results in dysfunctional TJs and subsequent microbial translocation in the host's tissues and organs.

Senotherapeutic drugs are comprised of senolytic agents (which promote the elimination of senescent cells) and senomorphic agents (which delete senescent markers). Senotherapeutics are underutilized in SCZ, but we believe they could be beneficial. For example, eliminating neurotoxic microglia could avert neurodegeneration and SCZ by sparing neuronal and glial cells.

Table 1. Common natural and synthetic senolytic and senomorphic drugs.

Senolytic drugs	Source	Mechanism	References
Kaempferol	Fruits and vegetables	GSK-3 beta inhibitor	78
Berberine	Oregon grape, phellodendron, and tree turmeric	Ceramide inhibitor	79.
Lycopene	Grape skin, guava, grapefruit, blueberries, and tomatoes	Scavenging of reactive oxygen species, enhancement of detoxification systems	80.
Fisetin	Strawberries, onions, apples, mangoes, persimmons, and kiwis	inhibiting the activity of nuclear factor-kappa B (NF-κB) and MAPK.	81
Senomorphic drugs			
Rapamycin	bacterium *Streptomyces hygroscopicus*	mTOR inhibition	82.
Acarbose	Soil bacteria	PPARγ upregulation	83.
SIRT-1	Grapes, berries, apples, and other fruits	Lowers oxidative stress	84
Fluvastatin and Valsartan	Synthetic	Increase telomerase activity	85.
KU-60019	Synthetic	Improves mitochondrial function	86.

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In the past, it was believed that cellular senescence was irreversible. However, newer studies have found that inhibiting 3-phosphoinositide-dependent protein kinase-1 (PDK1) can reverse this phenotype (87). For this reason, PDK1 inhibitors will likely play a significant role in SCZ.

Barrier Enhancers

Premature cellular senescence in SCZ affects most cell types, including those comprising the biological barriers. The senescent phenotype disrupts the TJs, enabling the translocation of gut bacteria into the host circulation. The GI tract barrier is comprised of epithelial and endothelial cells. IECs produce OXYTOCIN when prompted by secretin, a GI hormone the enterochromaffin cells produce. Earlier studies have associated secretin with symptomatic improvement of refractory SCZ, suggesting an indirect action via OXYTOCIN (88). Along this line, a recent study found that gut microbes influence OXYTOCIN release, implicating commensal flora in the biosynthesis of this hormone (89).

Indeed, it has been established that human commensal *Limosilactobacillus reuterii* produces OXYTOCIN, protecting the gut barrier (90). For this reason, probiotics with *L. reuterii* should be supplemented for SCZ patients. In addition, previous studies found that *Bifidobacterium breve A-1* ameliorated depression, anxiety, and cognition, combined with *L. reuterii*, could benefit SCZ. In addition, both microbes likely upregulate IL-22, "the guardian of the gut barrier," further averting microbial translocation (91).

During the HIV epidemic in the 1980s, IL-22 deficit was linked to increased intestinal permeability and HIV-induced massive translocation of gut microbes into host tissues. This occurred as the virus targeted innate lymphoid cells type 3 (ILC-3), producers of IL-22. Depletion of this cytokine led to microbial migration outside the gut lumen. For this reason, we proposed human recombinant IL-22 as a novel SCZ treatment (92). Other interventions for enhancing the gut barrier include serine proteases, such as nafamostat mesylate and camostat mesylate, known for decreasing paracellular spaces' size (93). Indigo and indirubin, Chinese herbal medicines, are enhancers of the gut barrier that are beneficial in IBD and probably SCZ.

OSU 03012 and Other PDK1 Inhibitors

Membranes separate body compartments, maintaining gradients and electrical charges that drive cellular machinery, ultimately making life possible. Plasma and organelle membranes comprise a lipid bilayer, and lipid peroxidation can alter the biophysical properties of membranes, disrupting the surface receptors and neurotransmission.

Due to their ability to reverse cellular senescence, PDK1 inhibitors are of extreme interest in SCZ, a disorder marked by premature aging and early mortality (94)(95). Indeed, several PDK1 inhibitors, including alpha-lipoic acid N acetylcysteine (NAC), have been found to lower lipid peroxidation and are currently being evaluated as SCZ treatments (96)(97(98)(NCT03788759).

Akt kinase is activated in cell membranes by PI3K, which stimulates PDK1, a master kinase recruited to the plasma membrane via its C-terminal pleckstrin homology (PH) domain. Interestingly, PH polymorphisms were previously associated with SCZ, further implicating PDK1 in this disorder (99).

The aging brain retains iron, which can enhance the oxidation of membrane lipid bilayer. This pathology could be ameliorated or reversed by MLR (101)(102)(103). Interestingly, aside from signaling with its receptors, DA also binds directly to membrane lipids, triggering peroxidation via 6-hydroxydopamine (6-OHDA), an established neurotoxin (104)(105).

We propose replacing oxidized membrane lipids with OSU 03012, a synthetic PDK1 inhibitor, and natural exogenous glycerophospholipids. We discussed MLR in other articles and will not repeat it here (Sfera A)(Del Campo CMZ). Initially described by Professor Garth Nicolson, who studied Gulf War Syndrome since 1990s, MLR was expanded to fatiguing disorders. We saw potential

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benefits of MLR in SCZ, a condition marked by premature cellular senescence and extensive oxidation of membrane lipids.

OSU-03012 is a celecoxib derivative that exerts antiproliferative, antibacterial, and antiviral properties and shares many characteristics of antipsychotic drugs (Table 2).

Table 2. OSU 03012 and antipsychotic drugs, common characteristic.

OSU-03012	Antipsychotic drugs	References
Lowers ER stress via PERK	Lower ER stress via PERK	106
Inhibits cathepsins	Inhibits cathepsins	107; 108
Antineoplastic properties	Antineoplasic properties	109;110
Antibacterial properties	Antibacterial properties	111, 112
Antiviral properties	Antiviral properties	113;114

Devoid any COX-inhibiting activity, OSU-03012 binds to and inhibits PDK1 (Figure 4) (115). Subsequently, the phosphorylation and activation of Akt are inhibited, disrupting the PI3K/Akt signaling pathway, a marker of tumorigenesis and SCZ.

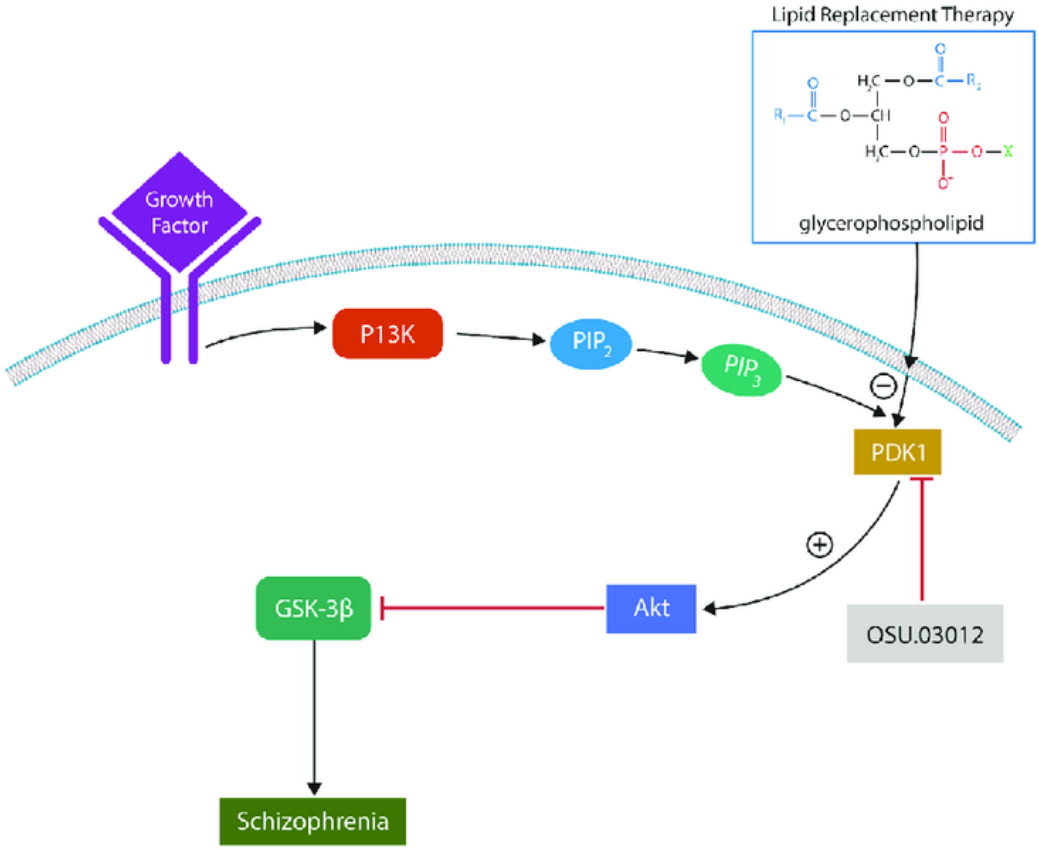

Figure 4. Upon growth factor-receptor binding, PDK-1 is recruited to the cell membrane and activated by PI3K via PIP1 and PIP2. MLR, especially the glycerophospholipid phosphatidylserine (PS), inhibits PDK1 by maintaining inactive conformation. Downstream, Akt phosphorylation is inhibited, releasing the inhibitory break from GSK-3β (lack of inhibitory phosphorylation). Together, phosphorylation changes contribute to neuropathology, including SCZ. Some second-generation

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antipsychotic drugs upregulate GSK-3β (by increasing activating phosphorylation). OSU-03012 acts synergistically with MLR, inhibiting PDK1.

Conclusions

Synthesized in the CNS and the gut, OXYTOCIN is far from only being the "hormone of love" and prosocial behaviors. In the GI tract, OXYTOCIN maintains the homeostasis of the gut barrier, preventing microbial translocation and likely improving the outcome of SCZ.

Interventions to upregulate OXYTOCIN, including senotherapeutics, AhR, and PDK-1 inhibitors, represent new strategies that could be helpful in SCZ and IBD. A particular intervention, MLR with OSU-03012 and human recombinant IL-22, may optimize the gut and BBB, eliminating the dormant CNS microbes.

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