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Review

Love in the Time of COVID: Psychiatric Outcomes Related to Oxytocin and the "Endocrine Organ"

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Abstract

The COVID-19 pandemic was an eye-opener for many medical disciplines. It highlighted viral exploitation of physiological cellular processes, including endocytosis and cellular senescence. These pathways play an essential role in cancer, neurodegenerative disorders, and schizophrenia (SCZ). Oxytocin, commonly called the "love hormone," is produced in the posterior hypothalamus and is crucial for various physiological processes, including social intelligence, sexual activity, and metabolism. Many viruses, including SARS-CoV-2, have been shown to inhibit the release of oxytocin from intestinal epithelial cells, thus hastening gut barrier senescence. Premature molecular aging at this level enables microbial migration outside the intestinal lumen, triggering inflammation and immunogenicity. The gut microbial community is immunologically tolerated within the gastrointestinal tract but can activate host immunity upon translocation. Immune responses to displaced commensals and/or their

components may contribute to neuroinflammation and gray matter volume reduction, a hallmark of severe mental illness. Oxytocin opposes microbial translocation into the systemic circulation through several mechanisms, including anti-inflammatory, tight junctions-upregulation, and suppression of senescence-associated secretory phenotype—the toxic secretome produced by senescent cells. *Limosilactobacillus reuterii,* a commensal microbe known for producing oxytocin, shows antiviral and anti-translocation effects, implying a beneficial role in schizophrenia. This condition has been linked to a dysfunctional gut barrier and increased microbial migration outside the intestinal lumen, suggesting that oxytocin replacement therapy could benefit patients with this mental illness. This review article summarizes the current understanding of oxytocin's role in schizophrenia and discusses natural and synthetic compounds that promote gut barrier homeostasis.

Keywords
Oxitocin; neuroinflammation; gut barrier; blood-brain barrier; schizophrenia

1. Introduction

Viruses, including SARS-CoV-2, exploit other signaling pathways, including hormones and neurotransmitters, for their benefit. For example, the Japanese Encephalitis Virus (JEV) usurps dopamine (DA) receptors to enter host cells, therefore disrupting dopaminergic signaling [1]. Oxytocin (OXT) signaling with OXT receptors (OXRs) is essential for fertility, integrity of biological barriers, and emotional and self-referential processing in the central nervous system (CNS) [2-4]. Interestingly, patients with SCZ exhibit disruption of the same functions, reflected in fewer offspring, increased microbial translocation, and impaired cognitive-emotional processing [5, 6]. Moreover, COVID-19 was associated with decreased birth rates and upregulated translocation markers and cases of new-onset SCZ, suggesting the intertwinement of underlying biological pathways [7-9].

The connection between viruses and severe mental illness has been documented for several decades. For example, women who were pregnant during the US rubella epidemic of 1964 gave birth to offspring that developed autism spectrum disorders (ASDs) or schizophrenia (SCZ) more often than the population at large, suggesting that many viruses, probably including COVID-19, may be associated with similar sequelae [10]. Other studies found that dormant viruses, such as human endogenous retroviruses (HERVs), could promote SCZ when activated by exogenous viral infections [11].

The gut microbes are known to produce most neurotransmitters and hormones generated by the host, so the microbiome is often conceptualized as the largest endocrine organ [12, 13]. Limosilactobacillus reuteri (*L. reuteri*), one of the OXT-producing gut microbes, has been less abundant in the human microbiome over the past two or three decades, probably accounting for the increased prevalence of autoimmune disorders, conditions linked to microbial translocation [14]. *L. reuteri* is found in the GI tract, urinary tract, skin, and breast milk and exerts anti-inflammatory, antimicrobial, and anxiolytic properties [15, 16].

OXT is a peptide hormone synthesized in the hypothalamic paraventricular (PVN) and supraoptic (SON) nuclei and stored in the posterior pituitary. In addition to *L. reuteri*, intestinal epithelial cells

(IECs) produce OXT when exposed to the GI tract hormone secretin [16]. This may explain the beneficial effect of secretin in refractory SCZ observed by earlier studies [17, 18]. OXT, implicated in social intelligence, signals with its receptors (OXRs) expressed throughout the brain [19-21].

The prosocial role of OXT and the fact that OXTRs are abundantly expressed in the insular cortex (IC) and anterior cingulate cortex (ACC) have led many researchers and clinicians to see a connection between OXT and the von Economo neurons (VENs) present in these areas [22, 23]. VENs are part of the salience network (SN), a neuronal assembly that shifts attention to relevant stimuli or from exteroception to interoception [24]. This is significant as several studies linked the central action of OXT to an enhanced gut barrier [25].

Aside from the role of OXT in maintaining the homeostasis of the gut barrier, this review examines novel SCZ interventions based on the microbial translocation hypothesis, including aryl hydrocarbon receptor (AhR) antagonists, senolytic agents, and recombinant human interleukin 22 (Il-22).

2. Cellular Senescence

The common denominator between virus-induced pathology and severe mental illness (SMI) is premature cellular senescence. A physiological or pathological response to stress, cellular senescence is a phenotype characterized by proliferation arrest, metabolic restructuring, and the release of a toxic secretome known as the senescence-associated secretory phenotype (SASP). This toxin, composed of cytokines, chemokines, growth factors, and enzymes such as matrix metalloprotease-9 (MMP-9), is known to disrupt tight junctions (TJs), particularly occludins and claudin-5, which maintain the physiological permeability of the gut barrier [26] (Figure 1).

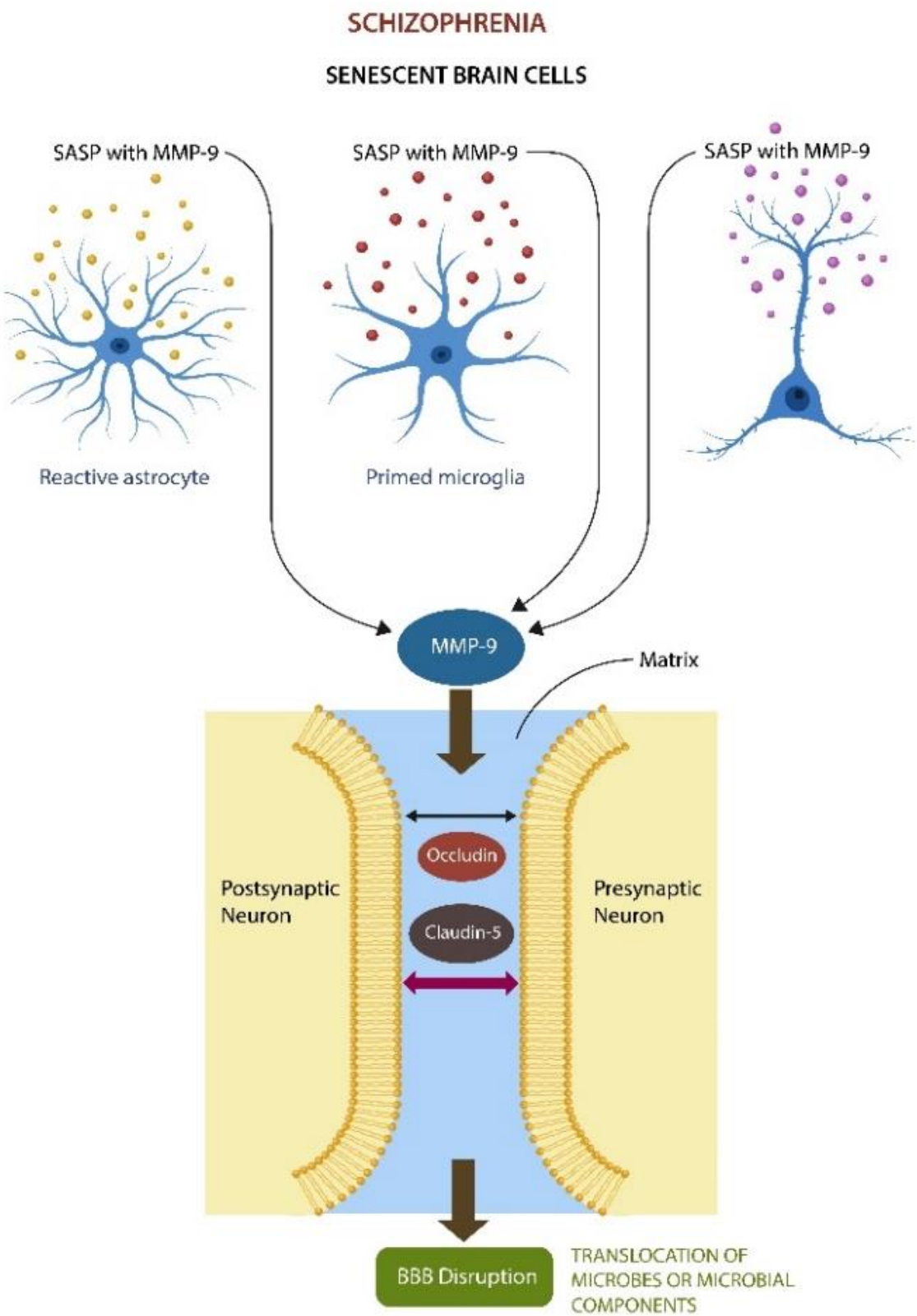

Figure 1 Senescent brain cells release SASP, a toxic secretome containing MMP-9. MMP-9 degrades tight junctions (TJs), increasing the gut and blood-brain barrier (BBB) permeability. This enables microbial translocation from the gut lumen into the systemic circulation, eventually reaching the brain. TJs, occludins, and claudins act like molecular Velcro, holding cells of biological barriers together. In SCZ and certain viral infections, MMP-9 is upregulated, facilitating microbial translocation.

Virus-induced senescence (VIS) refers to viral infections that can trigger premature cellular senescence in human tissues by damaging the genome or hijacking various signaling pathways, including MMP-9 [27].

Under physiological circumstances, somatic cells replicate 40-60 times, after which they undergo senescence. Exceptions to this rule are cancer cells and probably stem cells, which can divide indefinitely. Aside from replicative senescence, cells can activate the senescence program when in danger of malignant transformation or when they contain damaged DNA.

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

In patients with severe mental illness, the clearance of senescent cells 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 this disorder as a “segmental progeria” [28]. Along this line, telomeres are shorter in patients with SCZ, and senescent markers, such as p21, p16, and senescence-associated (SA)-β-galactosidase activity, are frequently elevated. On the other hand, OXT has been shown to improve social interaction and communication in children with autism spectrum disorders (ASD), highlighting a novel therapeutic strategy for this condition. Besides eliciting pro-social behavior, OXT exerts direct antiviral effects, particularly against the SARS-CoV-2 virus, as reported by several studies. Indeed, this action brought OXT into the research spotlight during the COVID-19 pandemic. OXT opposes cellular senescence, reduces SASP, and prevents the premature aging observed during the pandemic lockdowns [29]. OXT upregulates Claudin 5 and occludins, and suppressesMMP-9, reducing gut permeability [30, 31].

OXT receptors are abundantly expressed in the myenteric plexus of the GI tract and are involved in gut motility, anti-inflammatory actions, and barrier homeostasis. This suggests that cholinergic neurotransmission contributes to OXT release, likely explained by the activation of signal transducer and activator of transcription 3 (STAT3) [32]. In addition, as OXT upregulates interleukin (IL)-10, an anti-inflammatory cytokine that shares its receptor with IL-22, preventing translocation [33] (Figure 2). Moreover, like IL-22, OXT mediates wound healing, further substantiating the beneficial effect of this hormone on biological barriers.

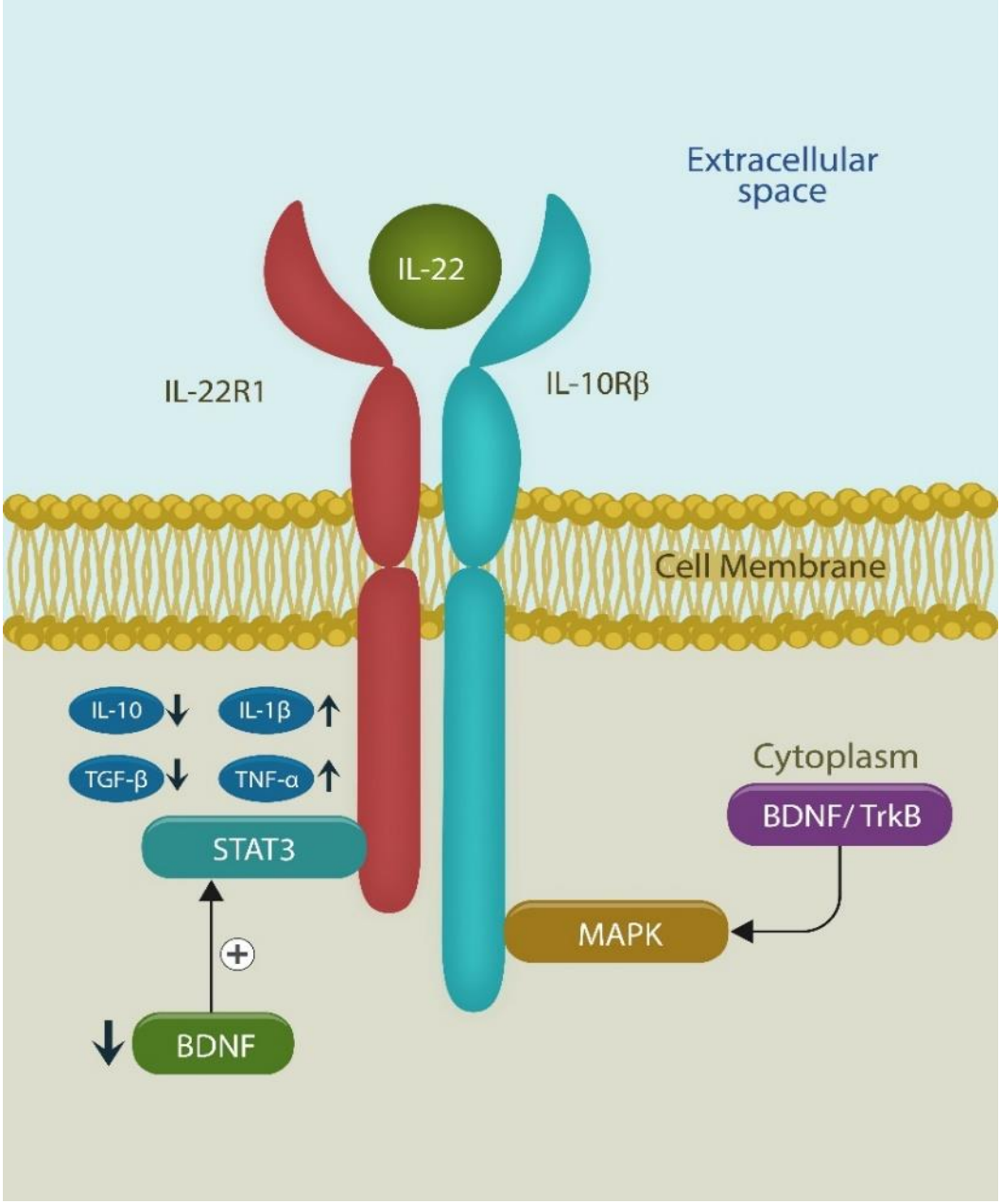

Figure 2 IL-10 and IL-22 utilize the same receptors (IL-10 receptor beta and IL-22 receptor 1). The binding of IL-22 to these receptors activates STAT3 and Mitogen-Activated Protein Kinase (MAPK). Reduced brain-derived neurotrophic factor (BDNF) enhances the cholinergic system-linked STAT3, especially in the insular and anterior cingulate cortex (IC) (ACC). BDNF binding to its receptor, TrkB, mitigates inflammation. Low BDNF levels elevate pro-inflammatory cytokines such as TNFα and interleukin 1 beta (IL-1β).

Due to SASP, cellular senescence maintains inflammation and neuroinflammation that drives gray matter volume (GMV) reduction, a hallmark of SCZ demonstrated by numerous neuroimaging studies (Table 1). GMV loss is in line with SCZ outcome studies, which show that only a minority of patients attain complete recovery after the first psychotic episode, suggesting that brain volume atrophy may progress despite the use of antipsychotic drugs [34]. White matter is also depleted in SCZ, although less than the gray matter, probably reflecting myelin damage.

Table 1 The molecular underpinnings of idiopathic (exemplified by SCZ) and virus-induced senescence (columns 1 and 2). Premature molecular aging leads to a dysfunctional gut barrier and BBB, which contribute to GMV reduction. Column 3 shows the opposing effects of OXT.

SCZ	VIRUS	OXT	References
Idiopathic senescence (SCZ)	Virus-induced senescence	Opposes senescence	[35-42]
Increased MMPI-9	Increased MMPI-9	Decreased MMP-9	[43-45]
Lowered Claudin-5 and Occludins	Lowered Claudin-5, occludins	Increased Claudin 5, and occludins	[46-50]
Gut barrier and BBB disruption	Gut barrier and BBB disruption	Lowers the permeability in the gut and BBB	[51-56]
Increased microbial translocation	Increased microbial translocation	Decreased microbial translocation	[57-59]
Decreased GMV	Decreased GMV	Increased GMV	[60-62]

GMV reduction in SCZ (occurring in medicated and unmedicated patients) has been associated with aggression and violence [63-65]. Conversely, OXT treatment may improve SCZ outcomes by preserving the GMV as documented in traumatic brain injury (TBI) [66, 67]. At present, SCZ outcomes (measured by sustained recovery after the first psychotic episode) are below 15%. In this regard, 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 [68-70]. These findings suggest that incorporating OXT into the standard SCZ treatment may enhance the overall outcome by preventing GMV reduction.

3. Senescent Microglia, Neuronophagy, and GMV Depletion

Premature microglial senescence may lead to aberrant activation of these cells and paradoxical neuronophagy (elimination of healthy neurons) [71, 72]. Microglia are brain-resident macrophages, vigilant cells that constantly scan the brain parenchyma and repair the damaged tissue, maintaining cerebral homeostasis [73].

Under physiological circumstances, senescent microglia can be adaptive, participating in tissue remodeling and repair. Both young and aged microglia respond to injuries, apparent molecular debris-induced inflammation, and damaged or senescent cells [74]. Dysfunctional senescent microglia may release pro-inflammatory cytokines and chemokines, contributing to chronic inflammation. These findings underscore the importance of more research on microglial phenotypes to develop novel therapeutic strategies for neuropsychiatric disorders. Indeed, aberrant neuronophagy by senescent microglia may play a significant role in developing age-associated neurodegenerative disorders and SCZ [75, 76]. For this reason, targeting senescent microglia and/or restoring the homeostasis of these cells could reduce neuroinflammation, neuronophagy, and GMV loss, potentially leading to improved outcomes in SCZ and neurodegenerative disorders.

In summary, the interplay between senescent microglia and neuronophagy is crucial for understanding the pathogenesis of several neuropsychiatric conditions and developing new treatment strategies.

4. The Role of Iron in Early Microglial Aging

The connection between senescence and iron accumulation is well-established. For example, intracellular iron levels 40 times higher were documented in senescent cells, linking aberrant neuronophagy to excess iron [77].

Furthermore, since reduced GMV has been directly correlated with aggressive behavior in neuropsychiatric disorders, abnormal iron levels in brain cells may drive both atrophy and violence. Indeed, like neuronophagy, ferroptosis, iron-induced cell death in the absence of lipid-repairing antioxidants, is a form of neuronal death without the involvement of glial cells [78]. On the other hand, iron accumulation in microglia, activation of these cells, and subsequent neuronophagy can also result in aggressive and violent behaviors [79].

A growing body of evidence supports that iron accumulation in senescent microglia activates these cells, triggering neurotoxicity, a phenotype known for eliminating viable neurons and synapses [80, 81]. Indeed, neurotoxic microglia engage in the phagocytosis of live neurons and convert astrocytes into neurotoxic cells, further contributing to GMV reduction.

Lysine lactylation (Kla) in histone proteins, a lactate-linked posttranslational modification, was demonstrated to play a key role in behavioral regulation [82, 83]. Lactate modulates iron metabolism via hepcidin, a liver hormone in charge of iron egress from hepatocytes and neurons [84]. In addition, a novel iron-histone pathway was recently described, further linking this biometal to lactylation, and aggression [84]. Lactylation appears to play a significant role in disseminating neurotoxicity from senescent microglia to astrocytes, bringing these brain macrophages into the arena of forensic psychiatry [85]. For example, iron as well as lactylation of histone 3 lysine 18 (H3K18) can trigger astrocytic neurotoxicity and subsequent reduction in GMV and emergence of violent behaviors [86]. Cellular senescence and SASP have been shown to promote cortical thinning, linking senescence to aggressive disturbances. In a previous article, we discussed ferosenescence, a phenomenon that is the opposite of ferroptosis [87]. In the brain, senescent neurons can undergo ferroptosis if astrocytes are damaged or ferrosenescence if astrocytes are viable and capable of supplying the neurons with the necessary antioxidants, such as glutathione peroxidase 4 (GPX4), ferritin, and “fresh” organelles, including mitochondria or lysosomes. The transfer of protective biomolecules from astrocytes to neurons through tunneling nanotubules (TNT) or extracellular vesicles (EVs) may prevent ferroptosis and enable the cell to thrive in ferrosenescenescence.

Recent studies have reported that antidepressant drugs, selective serotonin reuptake inhibitors (SSRIs) facilitate mitochondrial trafficking from astrocytes to neurons, linking major depressive disorder to low mitochondrial count [88] (Figure 3).

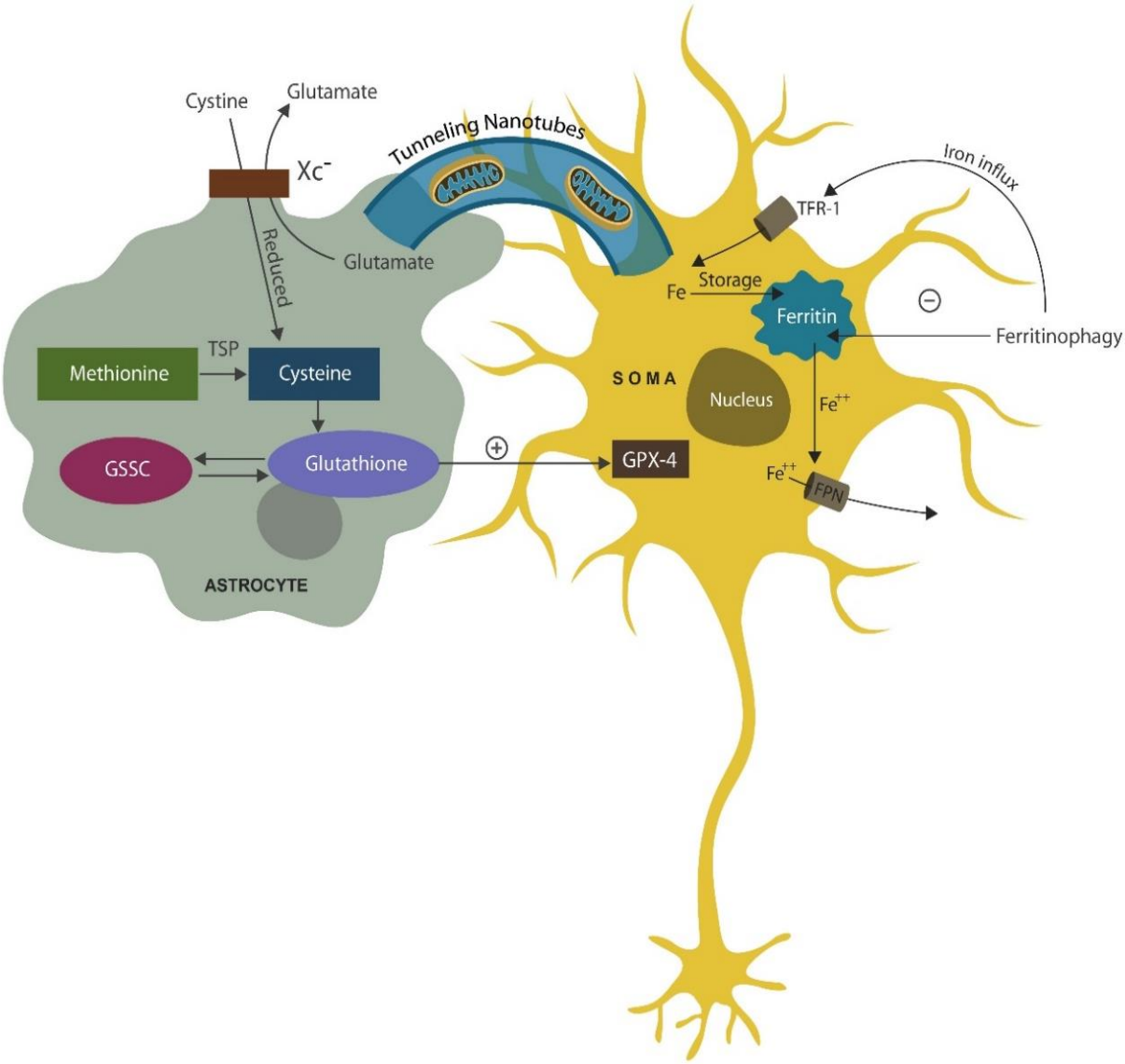

Figure 3 Among other supportive functions, astrocytes assist neurons by transferring fresh antioxidants like GPX4 and mitochondria. A recently discovered transfer modality, tunneling nanotubules, has been used to transport mitochondria and lysosomes from astrocytes to neurons.

5. Aryl Hydrocarbon Receptor, Iron, and Nutritional Immunity

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 neuropsychiatric arena. In addition, AhR is the master regulator of cellular senescence as it can sense endogenous and exogenous metabolites, xenobiotics, and toxicants.

AhR negatively regulates lactate and its posttranslational modification, lactylation. Consequently, dysfunctional AhR may drive premature neuronal and glial aging and the excessive lactylation documented in SCZ and other psychotic disorders [89].

Translocated microbes can trigger iron sequestration in host macrophages, a phenomenon known as nutritional immunity. Nutritional immunity aims to withhold iron from the invading pathogens, decreasing infectivity [90]. However, low circulatory iron often causes bacteria in host tissues, including the brain, to adopt a dormant phenotype, awaiting nutrient availability [91]. For example, dormant brain microbes were documented in Alzheimer's disease (AD), while a virome (viral microbiome) was recently identified in SCZ brains (Broadman area 46) [92-94]. The dormant microbes can be reactivated when iron becomes available, causing neuropathology. Moreover, iron regulatory proteins, including hepcidin, are AhR ligands, emphasizing a previously unknown relationship between AhR and nutritional immunity [92].

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 TJs, opening paracellular pathways utilized by microbes or their components to migrate outside the GI tract. In this regard, SCZ with negative symptoms was associated with antibodies against translocated *Hafnei alvei, Pseudomonas aeruginosa, Pseudomonas putida, and Klebsiella pneumonia*, which are proof of concept of microbial migration in this disorder [93].

Viruses also induce cellular senescence by manipulating AhR via viral antigens. For example, the SARS-CoV-2 virus usurps OXT via the OXT-activating motif found in calcium calmodulin kinase II (CaMKII), inducing senescence [94]. 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 OXT, further lowering the systemic level of this hormone [95].

Molecular imitation of placental proteins by viral arginine repeats, HAP2, tubulin, tau, and human endogenous retroviruses (HERVs) facilitates viral infection and the development of antibodies against host proteins, likely accounting for the reduced birth rates documented worldwide after the pandemic. Viral repeats (motifs) are known AhR activators, an action that manipulates AhR into adopting a pro-viral role. Activated AhR lowers interferon-gamma, a potent antiviral defense [96]. Therefore, AhR inhibitors exert not only anti-translocation but also antiviral properties.

6. Possible Interventions

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

6.1 Senotherapeutics

SCZ has been associated with premature molecular aging, which is reflected in decreased longevity 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 include senolytic agents (which promote the elimination of senescent cells) and senomorphic compounds (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 the healthy neuronal and glial cells (Table 2).

Table 2 Common natural and synthetic senolytic and senomorphic drugs that have been demonstrated to benefit both patients with schizophrenia and viral infections.

Senolytic drugs	**Source**	**Mechanism**	**References**
Kaempferol	Fruits and vegetables	GSK-3 beta inhibitor	[97]
Berberine	Oregon grape, phellodendron, and tree turmeric	Ceramide inhibitor	[98]
Lycopene	Grape skin, guava, grapefruit, blueberries, and tomatoes	Scavenging of reactive oxygen species, enhancement of detoxification systems	[99]
Fisetin	Strawberries, onions, apples, mangoes, persimmons, and kiwis	inhibiting the activity of nuclear factor-kappa B (NF-κB) and MAPK	[100]
Senomorphic drugs			
Rapamycin	bacterium *Streptomyces hygroscopicus*	mTOR inhibition	[101]
Fluvastatin and Valsartan	Synthetic	Increase telomerase activity	[102]
KU-60019	Synthetic	Improves mitochondrial function	[103]

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 [104]. For this reason, PDK1 inhibitors will likely play a significant role in future antipsychotic treatments.

6.2 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 can produce OXT in the presence of the gastric hormone secretin. Earlier studies have associated secretin with symptomatic improvement of refractory SCZ, suggesting an indirect action via OXT [88]. Along this line, a recent study found that gut microbes influence OXT levels, implicating commensal flora, including *Limosilactobacillus reuterii*, in the biosynthesis of this hormone [105, 106]. 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 poor cognition, suggesting that it could benefit SCZ in combination with *L. reuterii.* Furthermore, as both microbes likely upregulate IL-22, "the guardian of the gut barrier," they likely avert microbial translocation [107].

During the 1980s HIV epidemic, an IL-22 deficit was linked to increased intestinal permeability and HIV-induced translocation of gut microbes into host tissues. This occurred as the virus targeted innate lymphoid cell type 3 (ILC-3), the producers of IL-22.

Depletion of IL-22 led to microbial migration outside the gut lumen. For this reason, we have proposed human recombinant IL-22 as a novel SCZ treatment [108]. Other interventions for enhancing the gut barrier include serine proteases, such as nafamostat mesylate and campostat mesylate, which are known for decreasing paracellular spaces, thus lowering translocation [109]. Indigo and indirubin, Chinese herbal medicines, are enhancers of the gut barrier and have beneficial effects in IBD and probably SCZ.

6.3 OSU 03012 and Other PDK1 Inhibitors

Novel studies have demonstrated that aging cells can be "rejuvenated" via phosphatidylinositol-dependent kinase 1 (PDK1) inhibitors, including the BBB-crossing agent, OSU-03012 [110] (Figure 4). Aside from PDK1 inhibitors, inhibiting the downstream protein kinase B (Akt)/glycogen synthase kinase 3β (GSK3β) pathway may accomplish the same effect [111]. Indeed, many drugs, including some antipsychotics and lithium, inhibit GSK3β, suggesting that natural compounds exerting this effect may be beneficial against affective and psychotic disorders. For example, kaempferol, a polyphenol, and berberine, along with membrane lipid replacement (MLR), may exhibit antipsychotic properties [112, 113].

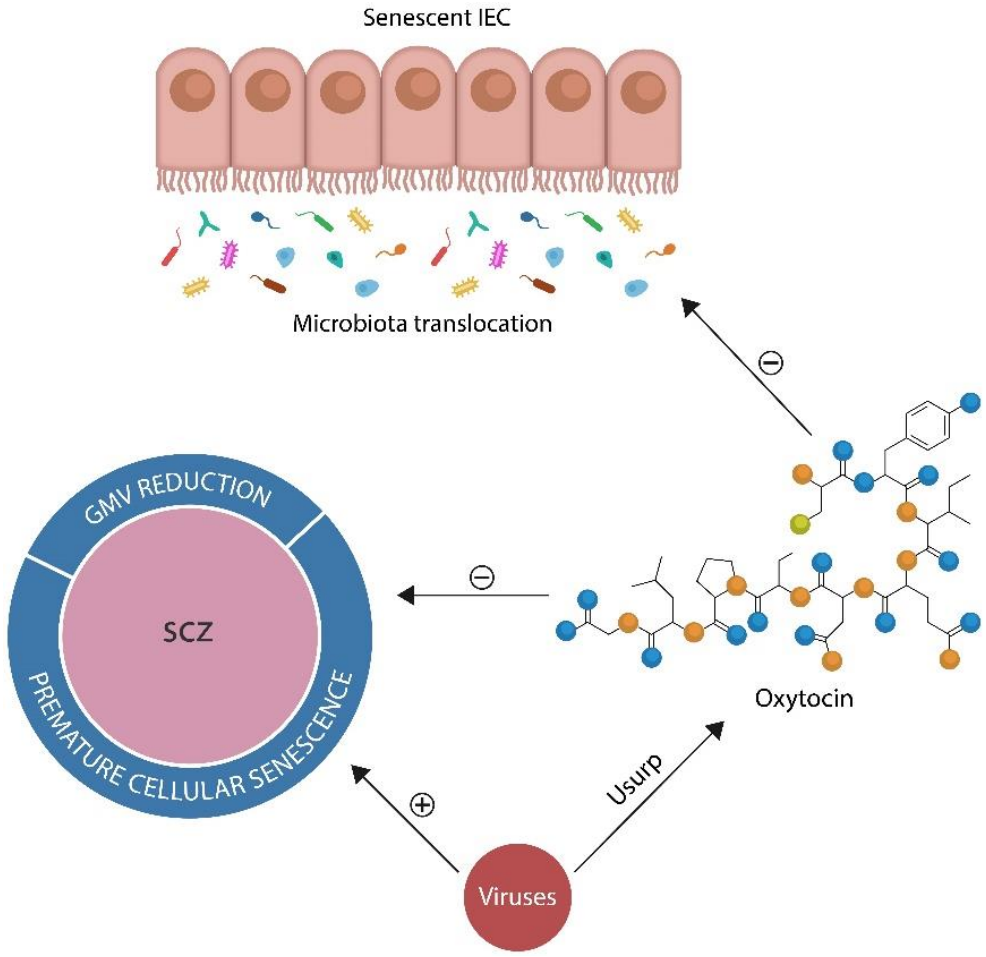

Figure 4 In the absence of OXT, senescent IECs enable microbial translocation outside the GI tract. Many viruses, including SARS-CoV-2, exploit OXT and promote VIS (virus-induced senescence). VIS, like SCZ, has been associated with GMC reduction and subsequent cognitive sequelae.

PDK1 inhibitors, including alpha-lipoic acid N acetylcysteine (NAC), have been found to lower lipid peroxidation and are currently being evaluated as SCZ treatments [114-117] (NCT03788759).

The aging brain retains iron, which can enhance the oxidation of the membrane lipid bilayer. This pathology could be ameliorated or reversed by membrane lipid replacement (MLR) [118-120]. Interestingly, aside from signaling with its receptors, DA also binds directly to membrane lipids, triggering peroxidation via 6-hydroxydopamine (6-OHDA), an established neurotoxin [121, 122].

We propose combining MLR with OSU 03012, a synthetic PDK1 inhibitor, a combination discussed in other articles that will not be repeated here [123] (Figure 5). Initially described by Professor Garth Nicolson, who studied Gulf War Illness since early 1990s, MLR was expanded to fatiguing disorders and SCZ, a condition marked by extensive oxidation of membrane lipids.

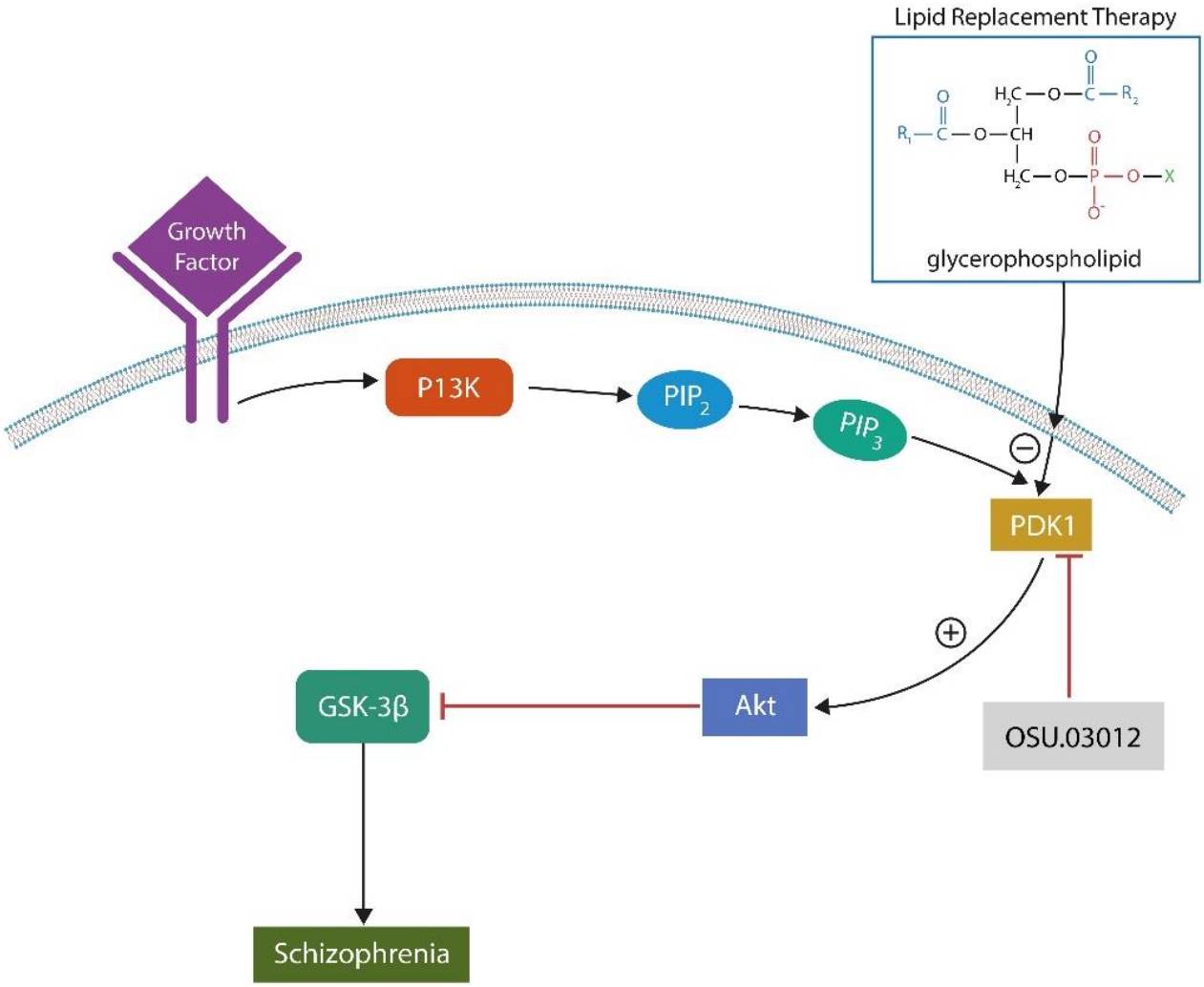

Figure 5 When the growth factor binds to its receptor, PDK-1 is recruited to the cell membrane and activated by PI3K through PIP1 and PIP2. MLR, particularly the glycerophospholipid phosphatidylserine (PS), inhibits PDK1 by maintaining its inactive conformation. Consequently, Akt phosphorylation is hindered, allowing GSK-3β to be released from inhibition. Some second-generation antipsychotic drugs upregulate GSK-3β by increasing its phosphorylation. OSU-03012 works synergistically with MLR to inhibit PDK1.

Interestingly, OXT inhibits the PI3K/AKT pathway, including PDK1, thus acting synergistically with PDK1 inhibitors. This suggests that combining this hormone with MLR could bring more benefit in SCZ than each component alone [124].

7. Conclusions

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

Interventions to upregulate OXT via AhR and PDK-1 inhibitors represent new treatment strategies applicable to SCZ and IBD. A particular intervention, combining OXT, MLR, OSU-03012, and human recombinant IL-22, may be beneficial by maintaining gut barrier homeostasis and eliminating already translocated microbes.

Author Contributions

Adonis Sfera: conceptualization and writing. Sabine Hazan: data curation. Jacob Anton: review, editing. Ioana Ciuperca: editing, supervision. Carolina Klein: editing, writing, and supervision. Karina G. Thomas: reviewing data.

Competing Interests

The authors have declared that no competing interests exist.

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