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REVIEW

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Lactoferrin for Mental Health: Neuro-Redox Regulation and Neuroprotective Effects across the Blood-Brain Barrier with Special Reference to Neuro-COVID-19

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ABSTRACT

Overall mental health depends in part on the blood-brain barrier, which regulates nutrient transfer in-and-out of the brain and its central nervous system. Lactoferrin, an innate metal-transport protein, synthesized in the substantia nigra, particularly in dopaminergic neurons and activated microglia is vital for brain physiology. Lactoferrin rapidly crosses the blood-brain barrier *via* receptor-mediated transcytosis and accumulates in the brain capillary endothelial cells. Lactoferrin receptors are additionally present on glioma cells, brain micro-vessels, and neurons. As a regulator of neuro-redox, microglial lactoferrin is critical for protection/repair of neurons and healthy brain function. Iron imbalance and oxidative stress are common among patients with neurodegenerative disorders such as Parkinson's disease, Alzheimer's disease, dementia, depression, and multiple sclerosis. As an endogenous iron-chelator, lactoferrin prevents iron accumulation and dopamine depletion in Parkinson's disease patients. Oral lactoferrin supplementation could modulate the p-Akt/PTEN pathway, reduce Aβ deposition, and ameliorate cognitive decline in Alzheimer's disease. Novel lactoferrin-based nano-therapeutics have emerged as effective drug-delivery systems for clinical management of neurodegenerative disorders. Recent emergence of the *Coronavirus disease-2019* (COVID-19) pandemic, initially considered a respiratory illness, demonstrated a broader virulence spectrum with the ability to cross the blood-brain barrier and inflict a plethora of neuropathological manifestations in the brain – the *Neuro*-COVID-19. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections are widely reported in Parkinson's disease, Alzheimer's disease, dementia, and multiple sclerosis patients with aggravated clinical outcomes. Lactoferrin, credited with several neuroprotective benefits in the brain could serve as a potential adjuvant in the clinical management of *Neuro*-COVID-19.

KEYWORDS

Alzheimer's disease; brain tumor; blood-brain barrier; COVID-19; Lactoferrin; mental health; neurological symptoms; Neuro-COVID-19; Parkinson's Disease; Redox; SARS-CoV-2

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Introduction

Mental health relates to our emotional, psychological, and social well-being. It affects how we think, feel, and act – a *Mind/Body Connection* – and also helps to determine how we handle stress, relate to others, and make choices (U.S. Department of Health and Human Services (DH&HS)), 2020). Mental health is important at every stage of life, from childhood and adolescence through adulthood. In 2019, an estimated 51.5 million adults aged 18 or older in the U.S. were reported to have 'any mental illness' (AMI) and this count represents 20.6% of all U.S. adults. The prevalence of AMI was higher among women (24.5%) than men (16.3%) (U.S. National Institute of Mental Health (NIMH)), 2019). Mental illnesses, such as depression, are the third most common cause of hospitalization in the U.S. for those aged 18-44 years old, and adults living with serious mental illness die on average 25 years earlier than others (Kessler et al. 2007).

Several factors are known to affect mental health, including but not limited to genetics and brain chemistry; life experiences, such as trauma or abuse; family history of mental disorders; as well as lifestyle choices including diet, physical activity, and substance use. Poor mental health is associated with an increased risk of stroke, type 2 diabetes, and heart disease. The global burden of mental illness accounts for 32·4% of 'years lived with disability' (YLDs) and 13·0% of 'disability-adjusted life-years' (DALYs). These estimates place mental illness a distant first in global burden of disease in terms of YLDs, and level with cardiovascular and circulatory diseases in terms of DALYs (Vigo et al. 2016).

The *Blood-Brain Barrier* (BBB) is the body's designated 'gatekeeper' that strictly regulates nutrient transfer in-and-out of the central nervous system (CNS). Therefore, the mere presence of a single or combination of potentially therapeutic nutrients do not necessarily ensure its transport across the BBB and delivery to its tissue target – the brain, unless there is a specific carrier system. In fact, only a selective class of circulating molecules possess the unique ability to cross the BBB (Campos-Bedolla et al. 2014). Lactoferrin (LF), an innate metal-chelator is one such physiological carrier system to transport bioactive molecules across the BBB.

Lactoferrin (LF) is a non-heme ∼80 kDa iron-binding antimicrobial glycoprotein composed of 703 amino acid residues present in most exocrine secretions that bathe mammalian mucosal surfaces (Naidu 2000; Lönnerdal 2009; Legrand 2016). As a member of the transferrin family, at the amino acid level LF shares more than 60% homology with transferrin (TF). LF is synthesized by activated microglial cells in specific areas of the brain and has been credited with multiple neuroprotective benefits (Fillebeen et al. 1999). Several studies have confirmed the ability of LF to cross the BBB (Ji et al. 2006); a rapidly growing body of evidence also demonstrates the ability of LF to act an effective carrier molecule to facilitate transfer of other therapeutic agents across the BBB (Huang et al. 2013; Singh et al. 2016; Elzoghby et al. 2020).

Interactions of LF with specific mammalian cell receptors play a pivotal role in mediating multiple functions of this iron-binding glycoprotein (Naidu 2000, Suzuki et al. 2005). LF-binding receptors (LFRs) have been identified in various types of cells such as lymphocytes, hepatocytes, and enterocytes (Suzuki et al. 2005). LF is shown to enhance iron status of infants and pregnant women, *via* an LFR-mediated pathway. LF is

absorbed in intact form *via* an intestinal LFR and transported into the blood circulation (Matsuzaki et al. 2019). In addition, LF can stimulate intestinal cell proliferation and differentiation, causing expansion of tissue mass and absorptive capacity (Lönnerdal 2009).

COVID-19 and mental health

Indirect emotional outcomes of the COVID-19 pandemic include distress, anxiety, uncertainty, depression, and insomnia in the general population and among healthcare professionals (Brooks et al. 2020). Specific stressors including social isolation, fear of infection, chronic stress and economic difficulties may lead to development or exacerbation of substance abuse and other psychiatric disorders in vulnerable populations. Mental health consequences of the COVID-19 crisis such as increases in suicidal tendencies for an extended time post-pandemic have also been demonstrated (Sher 2020). In addition to these indirect pandemic-associated psychological distresses, direct effects of COVID-19 and its subsequent effects on host immune response (i.e. cytokine storm) significantly impact many organ-specific manifestations, given that ACE-2 receptors are expressed in multiple extra-pulmonary tissues including the cerebral cortex and brainstem. (Gupta et al. 2020; Tay et al. 2020; Zubair et al. 2020). Altered mental status has been reported to be the second most common complication identified post-COVID-19 infection, often occurring in younger patients. (Varatharaj et al. 2020). A recent systematic review suggests that COVID-19 may exacerbate neurological symptoms in patients with preexisting mental illness. In particular, 60% of patients with PD or dementia exhibit exacerbation of preexisting neurological symptoms.(Kubota and Kuroda 2021).

LF and COVID-19

Recently, our research group, as well as other laboratories in Europe and Asia, have elucidated a broad-spectrum antiviral activity for LF against COVID-19 infections (Campione et al. 2020; Chang et al. 2020; Naidu et al. 2020b). In an observational study, COVID-19 patients ($n = 75$) treated for 10 days with oral administration (4 to 6 doses/day) of liposomal bovine LF (32 mg) + vitamin-C (12 mg), and zinc (10 mg: 2 to 3 doses/day) showed a complete recovery in all patients (100%) within the first 4-5 days. Similar treatment with one-half the dose administered to the COVID-19 patients prevented transmission to healthy individuals in direct contact with the affected patients (Serrano et al. 2020). Based on such ongoing field observations, this narrative review is an attempt to elucidate the integral role of LF in various pathways of brain physiology and pathology. Considering that neurological disorders are well recognized comorbidity factors for COVID-19 infection, the interventional spectrum of LF to control the pandemic from a mental health perspective is discussed.

LF distribution in the central nervous system (CNS)

LF is present in several types of neurons, synthesized in specific areas of the brain, such as the normal substantia nigra, particularly in the dopaminergic (DA)-neurons and

specific glial cells (Kawamata et al. 1993). *In situ* synthesis of LF occurs in brain, and LF transcripts have been detected in human (Siebert and Huang 1997) and mouse brain tissues (Fillebeen et al. 1998). LF expression is up-regulated in mouse brain tissue treated with MPTP (*1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine*), a neurotoxin for inducing Parkinson's Disease (PD) (Fillebeen et al. 1998). Upregulation of LF, however, does not fully explain the large increase of LF levels during neurodegenerative disorders (Leveugle et al. 1994; 1996). Studies with normal, aged, and MPTP-treated mice showed LF expression on micro-vessels in cerebral cortex (Fillebeen et al. 1999). LF was detected in the hippocampus region of aged mouse brains, exclusively in pyramidal neurons and fibers. No upregulation of LF was found during the aging process. Interestingly, brain stressed with MPTP increased expression of both LF and redox enzymes (i.e. *catalase* and *γ-glutamylcysteine synthetase*) that scavenge harmful free radicals including reactive oxygen/nitrogen species to protect brain tissue from oxidative damage (Fillebeen et al. 1999). LF administration (2.0-g/kg/day for 3 months) in aged mice, improved spatial cognition with more pyramidal cells detected in the hippocampus. LF also reduced iron deposition, malondialdehyde (MDA) and levels of reactive oxygen species in the hippocampus (Zheng et al. 2020).

LF accumulates in specific regions of the brain such as mesencephalon that are adversely affected with neurodegenerative disorders (Osmand and Switzer 1991; Kawamata et al. 1993; Leveugle et al. 1994). In the cerebrospinal fluid (CSF), LF levels are elevated in acute cerebrovascular lesions (Terent et al. 1981; Hällgren et al. 1982). In the mesencephalon, LF is found in the DA-neurons; however, the surviving neurons accumulate higher concentrations of LF during PD (Faucheux et al. 1995; Leveugle et al. 1996). LF is shown to decrease the *brain-derived neurotrophic factor* (BDNF) levels in the hippocampus and seem to improve depressive-like symptoms in a repeated forced-swim test (FST) stressed mouse model (Takeuchi et al. 2017).

LF and early brain development

LF is considered as a conditional nutrient for neurodevelopment and neuroprotection, during the neonatal phase of rapid brain growth (Wang 2016). The multifunctional benefits of LF in neonatal food supplementation include: i) upregulation of canonical signaling pathways for neurodevelopment and cognition; ii) modulation of BDNF signaling pathway in the hippocampus; iii) upregulation of polysialic acid expression, a marker of neuroplasticity, cell migration and differentiation of progenitor cells, and the growth/targeting of axons; iv) upregulation of transcriptional and translational levels of BDNF and increased phosphorylation of the *cyclic Adenosine Mono-Phosphate* (cAMP) Response Element-Binding (CREB) protein, a downstream target of the BDNF signaling pathway. CREB is a protein of critical importance in neuro-development and cognition; and v) enhance cognitive function and learning (Chen et al. 2015). A high incidence of neurodevelopmental disabilities in premature infants has been attributed to cerebral hypoxia-ischemia (CHI) from brain injury. In an experimental murine CHI model, LF supplementation showed neuroprotective benefits on brain metabolism, as well as recovery of cerebral gray and white matter. LF intervention seems promising for clinical management of preterm infants with CHI (van de Looij et al. 2014).

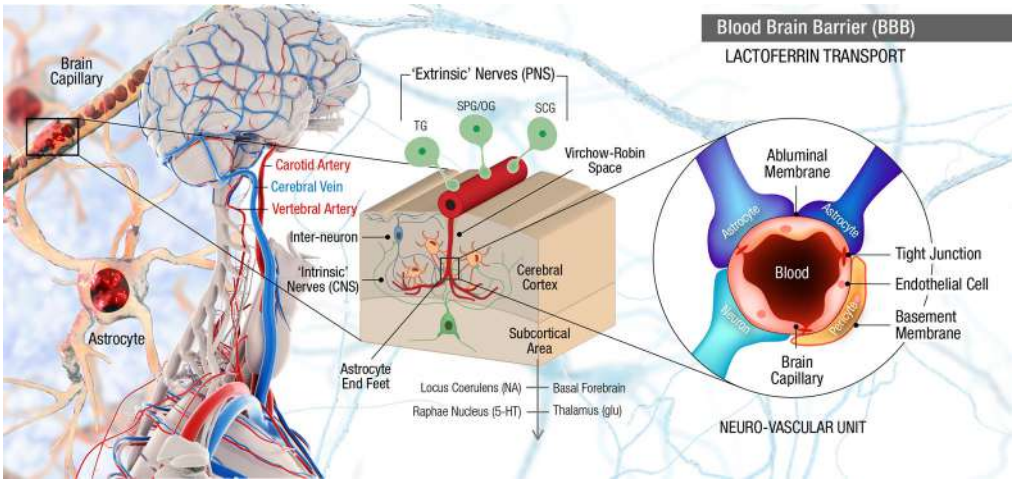

Figure 1. The Blood-Brain Barrier (BBB) is established by specialized endothelial cells (ECs) sealed by continuous complex of tight junctions to form a polarized barrier. The BBB restricts the free exchange of most solutes between plasma and the extracellular fluid of the brain. The brain capillary ECs have no direct trans-endothelial passageways such as fenestrations or channels; however, specific transport mechanisms located in the cerebral ECs ensure that the CNS gets an adequate supply of nutrients.

LF transport across blood-brain barrier (BBB)

The BBB is a unique dynamic regulatory interface located at the border between the blood stream and the brain. The BBB protects the brain against circulating toxins or pathogens that could potentially cause infections. As the 'gatekeeper' for the CNS, BBB facilitates uptake of vital nutrients, vitamins, and hormones to sustain cerebral growth and metabolism, as well as maintains cerebral ionic and volume balance (Keep et al. 1998). Our knowledge of the BBB has evolved dramatically over the past 20 years from a simple restrictive interface that impedes the diffusion of polar solutes to brain, to a dynamic, highly selective, regulatory interface that expresses a plethora of specific transport systems in response to milieu changes and maintain optimal cerebral homeostasis (Sharif et al. 2018).

Blood brain barrier (BBB): Structure-Function

The BBB is established by specialized endothelial cells (ECs) sealed by a continuous complex of tight junctions to form a polarized barrier. The BBB restricts free exchange of most solutes between plasma and the extracellular fluid of the brain. The blood capillary ECs (BCECs) have no direct trans-endothelial passageways such as fenestrations or channels; however, specific transport mechanisms located in the cerebral endothelia ensure an adequate supply of nutrients to the CNS (Figure 1).

Most plasma proteins are unable to cross the BBB due to size exclusion and hydrophilic nature. A few specific proteins such as LF, insulin, insulin-like growth factors and vasopressin are known to cross the BBB by receptor-mediated transcytosis (Laterra et al. 1999). ECs that line the inner walls of blood vessels facilitate the internalization and transportation of bioactive molecules across the BBB. For example, insulin is

rapidly transported across BCECs by a receptor-mediated process with minimal degradation (King and Johnson 1985). The iron-transferrin (TF)-complex, an iron-binding protein cluster similar to LF, is transported across the BCEC through receptor-mediated transcytosis without degradation. The BCECs have specific high-affinity TF-binding sites ($K_D = 11.3 \pm 2.1$ nM; $n = 3.5 \times 10^4$ receptors/cell) (Descamps et al. 1996).

LF receptors in brain cortex and transcytosis

LF crosses the BBB *via* receptor-mediated transcytosis (Ji et al. 2006). Differentiated BCEC have specific high-affinity ($K_D = 37.5$ nM; $n = 9 \times 10^4$ receptors/cell) and low-affinity ($K_D = 2\,\mu$M; $n = 90 \times 10^4$ receptors/cell) LF-binding sites. Surface-bound LF is internalized *via* specific uni-directional receptor-mediated transport with no apparent intra-endothelial degradation. Iron may cross the BCEC as a covalently bound complex with LF protein. The low-density lipoprotein (LDL) receptor-related protein inhibits 70% of LF transport; therefore, the LDL receptor-related protein is an antagonist for the LF-mediated iron sequestration (Fillebeen et al. 1999). LF is rapidly transported into the brain and accumulates in the cytoplasm of vascular endothelial cells in the neocortex, striatum, hippocampus, and thalamus (Kopaeva et al. 2019). LF, compared to TF, is more rapidly eliminated from the blood (half-life of LF is about 8 and six times shorter than that of TF) (Ji et al. 2006).

LF binding to specific receptors on human intestinal brush border stimulates proliferation and differentiation of small intestinal epithelial cells; therefore, affects mass, length, and epithelial digestive enzyme expression of the small intestine. A 105-kDa LF receptor (LFR) specifically mediates LF uptake into enterocytes and crypt cells on intestinal brush border (Lönnerdal 1991). The complex of LF and LFR is internalized through clathrin-mediated endocytosis; both iron-free apo-LF and iron-saturated holo-LF activate the PI3K/Akt pathway, whereas only apo-LF triggers ERK1/2 signaling (Liao et al. 2012).

Similarly, LF binding receptors (i.e. LFRP1 and LFRP2) have also been identified on glioma cells, brain micro-vessels and neurons (Suzuki et al. 2005). The cationic (+ve) nature of LF protein at physiologic pH allows rapid charge transfer of this molecule across the anionic (-ve) lipid membranes of BCEC. These distinct physio-chemical attributes make LF an efficient endogenous transport module for target delivery of drugs, genes, and bioactive molecules across the BBB (Elzoghby et al. 2020).

Activated microglia trigger LF release

Microglial cells are resident macrophages of CNS, critical for host defense against pathogens and to clear debris from damaged cells. These immune cells also interact with neurons at physiological conditions and modulate the fate and function of synapses. Microglial cells invade the CNS during early embryonic development and influence cellular proliferation, migration, and differentiation as well as the formation and maturation of neuronal networks (Mosser et al. 2017). Microglia maintain the CNS by constantly scavenging the plaques, damaged or unnecessary neurons and synapses, and

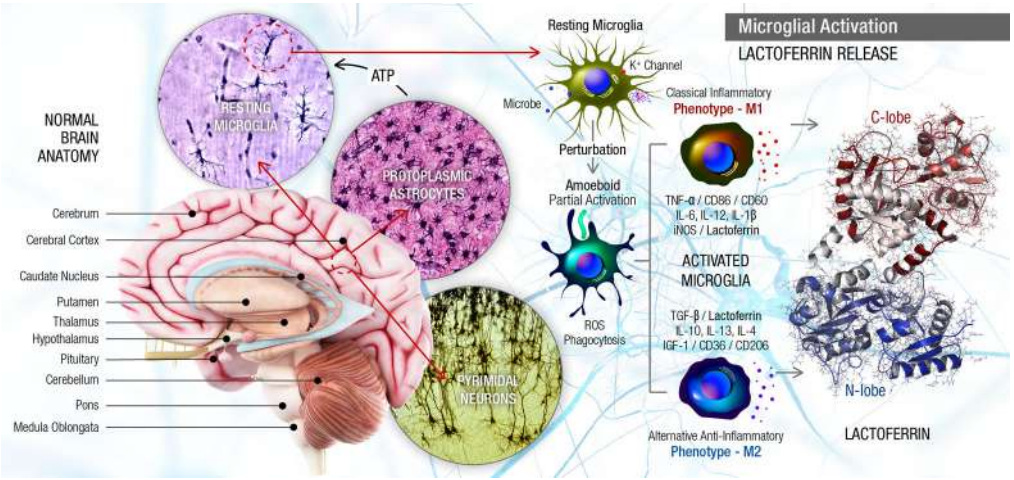

Figure 2. Microglia, under normal physiological conditions, remain in the resting phenotype with neuronal activities such as synaptogenesis, neurogenesis and release of neurotrophic factors. Microglia are activated after exposure to pathogen-associated molecular patterns (PAMPs) and/or endogenous damage-associated molecular patterns (DAMPs), and removal of the immune-suppressive signals. Activated microglia secrete LF, proinflammatory cytokines, chemokines, and reactive oxidants.

infectious agents. Microglia continuously monitor neuronal functions through direct somatic interactions and provide neuroprotection (Cserép et al. 2020).

LF release by microglia

Activated microglia trigger the synthesis of LF, pro-inflammatory and anti-inflammatory cytokines to protect the CNS from microbial pathogens and toxic insults (Fillebeen et al. 2001; Aguilera et al. 2018). Microglial cells during activation may also generate free radicals and other highly reactive oxygen and nitrogen species (i.e. $O_2^{\bullet -}$, H_2O_2, $^{\bullet}OH$, and $NO^{\bullet}$) that may cause oxidative damage to neurons. Therefore, microglia are equipped with efficient free radical and oxidant scavenging mechanisms such as glutathione (GSH), and redox enzymes including superoxide dismutase (SOD), catalase, GSH-peroxidase, and GSH-reductase, as well as NADPH-regenerating enzymes (Dringen 2005). Any decline in redox enzymes could result in increased free radical/oxidant levels that result in lipid peroxidation, protein oxidation, and oxidative damage of nucleic acids. While moderate oxidation triggers apoptosis, severe oxidative stress could lead to tissue necrosis or even cellular death (Davies 1995; Naidu 2013; Sies 2017). Interestingly, when the brain is stressed, the increased expression of LF coincides with elevated levels redox enzymes (Fillebeen et al. 1999) (Figure 2).

Release of microglial-LF along with proinflammatory cytokines, chemokines, and reactive oxidants serve a neuroprotective role in the CNS (Fillebeen et al. 2001). As one of the early inflammatory mediators, LF helps to combat pathogens and contributes to the activation of innate host defense *via* regulation of adaptive immune pathways (Siqueiros-Cendón et al. 2014). In concert with immune co-factors, microglial-LF also modulates chemokine release and lymphocyte migration to amplify defense mechanisms

in the CNS. Therefore, LF is fundamental for redox homeostasis of microglia, a pre-requisite milieu balance for protection/repair of neurons for healthy brain function.

LF and neuro-redox

Brain activity is a high-energy demanding process that involves recruitment and adaptation of neuronal cells for active metabolism, while sustaining energy and redox homeostasis. Neurotransmission generates mitochondrial reactive oxygen species (ROS) and reactive nitrogen species (RNS) in neuronal cells (Bolaños 2016). All metabolic events that yield ROS, RNS, and other reactive intermediates cumulatively establish the redox (**red**uction-**ox**idation) state in the CNS. Low amounts of ROS/RNS generated by each neuronal cell are important mediators in redox signaling processes; however, any imbalance in redox homeostasis (generation vs. elimination of ROS/RNS) leads to oxidative/nitrosative stress, causing severe damage to neuronal cell systems. In the CNS for example, cerebral vasculature, which is critical for the BBB function, is particularly susceptible to oxidative stress (Lehner et al. 2011).

Neuro-redox represents the vital pathways of energy transfer in the CNS. Any disruption to the neuro-redox state could trigger and/or aggravate pathogenesis of several brain diseases. Furthermore, neuro-redox is fundamental for the development, function, and aging of the CNS. Neuro-redox transmits specific cell signals that regulate a myriad of neurological processes including neurotransmission, homeostasis, and degeneration (Naidu 2013; Franco and Vargas 2018). Neuro-redox is fundamental for neuronal cell metabolism and regular brain function.

LF and neuro-redox regulation

In human body, the free available iron levels must be maintained below 10^{-18} M to avoid microbial infections and to avoid precipitation of insoluble ferric hydroxides as well as the generation of harmful free radicals *via* the Fenton reaction (Thomas et al. 2009). In the brain, the neuroglia (astrocytes and microglia) release neuroprotective substances, such as LF, glutathione (GSH), and redox enzymes in response to cell signals and activation (Fillebeen et al. 2001). The iron-binding abilities of LF help regulate free bioavailable iron levels within 10^{-18} M (Klebanoff and Waltersdorph 1990; Naidu 2000). Binding of LF to Fe^{3+} ions blocks iron-mediated catalysis and oxidative disturbances in the CNS. Any imbalance in iron homeostasis, and ensuing oxidative stress contribute to neurodegeneration. For example, iron could interact directly with Aβ-peptide, the main component of β-amyloid lesions in Alzheimer's disease (AD). Also, insoluble amyloid plaques in postmortem AD brain are abnormally enriched with Fe^{3+}, Cu^{2+}, and Zn^{2+} (Huang et al. 2004). The iron-binding and metal-sequestration ability of microglial-LF could prevent oxidation of lipids, proteins and nucleic acids. Accordingly, LF may reduce oxidative stress at the molecular level, and modulate inflammatory responses at the tissue level (Volden et al. 2012). As a regulator of neuro-redox homeostasis, microglial-LF is critical for protection/repair of neurons and healthy brain function.

Neuro-redox and circadian rhythms

Cellular redox state undergoes a ~24-h (circadian) oscillation in most tissues, including the brain. In the suprachiasmatic nucleus (SCN), a hypothalamic region of the brain specialized for circadian timekeeping, redox oscillation modulates neuronal membrane excitability. The SCN redox environment is relatively reduced in daytime when neuronal activity is at its highest and relatively oxidized in nighttime when activity is at its lowest (Bothwell and Gillette 2018). The redox state directly modulates SCN K^+ channels, tightly coupling metabolic rhythms to neuronal activity. Application of reducing or oxidizing agents produces rapid changes in membrane excitability in a time-of-day-dependent manner.

Patients with cerebral degenerative conditions commonly suffer from a variety of circadian rhythm disturbances and sleep disorders, including sleep-disordered breathing, insomnia, parasomnias (REM sleep behavior disorder), and restless legs syndrome (RLS). Iron deficiency is considered a putative cause for RLS, a human sensorimotor disorder characterized by a circadian presentation of symptoms during the evening hours that disrupts one's ability to sleep (Dean et al. 2006). Patients with RLS have lower levels of dopamine in the substantia nigra and respond to iron administration (Patrick 2007). LF plays a central role in iron homeostasis in the CNS and in maintaining the circadian rhythm.

LF for target-delivery of therapeutics across BBB

The BBB and its restricted permeation of molecules into the brain limits the bioavailability and efficacy of drugs for CNS therapy. Low pinocytic activity at tight junctions and efflux pumps with inactivating enzymes in BCEC, also limit the permeation of molecules across the BBB (Kabanov and Batrakova 2004). Drug re-engineering with endogenous transporter molecules localized in BCEC may help overcome the BBB barricade (Pardridge 2007). LF binds to specific ligands on BCEC surface and transports the covalently bound molecules across the neuronal cell membrane *via* receptor-mediated transcytosis. Therefore, LF offers an active nanocarrier target-delivery system for transport of therapeutics across the BBB (Huang et al. 2007). In contrast to TF, the low plasma levels of endogenous LF, with its positive charge and unidirectional transport across the BCEC membrane provides an advantage for increased brain accumulation of LF-conjugated delivery modules (Fillebeen et al. 1999). Accordingly, LF-conjugated systems show 2.2-fold higher uptake and 2.3-fold elevated brain gene expression in BCECs compared to TF (Huang et al. 2008).

Due to its specific receptor-mediated targeting on luminal side of the BBB, LF could also deliver nuclear imaging probes and facilitate diagnosis of neurodegenerative diseases (Huang et al. 2013). LF-based molecular 'Trojan horses' are available with fusion protein technology to target the brain with therapeutic drugs or cognitive health nutrients. LF-conjugated polyethylene-glycol (PEG) liposomes or solid lipid nanoparticles (SLN) show efficient diffusion of molecules across the BBB and provide potent target delivery of diagnostics or therapeutics for various brain conditions (Huang et al. 2013; Singh et al. 2016). LF-based nano-therapeutics are emerging as effective systems

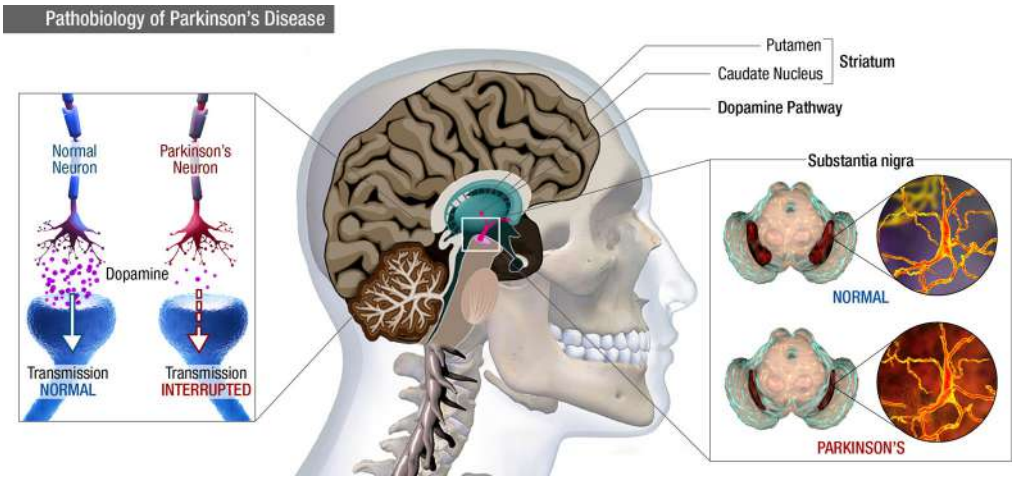

Figure 3. The pathobiology of Parkinson's disease (PD) includes DA-neuronal degeneration in the substantia nigra, and major reduction of dopamine content in the striatum. With progression of PD, the pathology spreads to neocortical and cortical regions of the brain. Iron-sequestration by LF prevents iron-catalyzed oxidative stress and protect DA-neurons from apoptosis.

for clinical management of anti-PD, anti-AD, anti-tumor and other neurodegenerative brain disorders (Elzoghby et al. 2020).

LF and brain pathology

Iron (Fe^{3+}) is a crucial element for brain metabolism. Iron serves as an electron acceptor and donor, vital for various cellular metabolic processes such as oxidative phosphorylation and energy production in mitochondria. Therefore, optimum iron transport across BBB and maintenance of Fe^{3+} level in the brain parenchyma require strict regulation for neuronal homeostasis. However, any change in iron levels may cause malfunctions in the brain. For instance, in case of Parkinson's disease (PD), Alzheimer's disease (AD) and other neurodegenerative disorders, an abnormally elevated Fe^{3+} levels are reported in the brain (Jiang et al. 2017). During neurodegenerative disorders, excess iron load with LF, but not TF, is evident in the affected regions of the brain. This observation suggests that LF plays a critical role during neurodegenerative diseases (Khan et al. 2020).

LF and Parkinson's disease (PD)

Parkinson's disease (PD) is a neurodegenerative disorder that affects ~1% of the population above 60 years of age. The main neuropathological criteria is *α-synuclein*-containing Lewy bodies and loss of dopaminergic (DA)-neurons in the substantia nigra. With progression of PD, Lewy body pathology spreads to neocortical and cortical regions of the brain. PD is regarded as a movement disorder with three cardinal signs: tremor, rigidity, and bradykinesia (Obeso et al. 2017; Tysnes and Storstein 2017). The pathobiology of PD includes DA-neuronal degeneration in the substantia nigra, and significant reduction of dopamine content in the striatum (Figure 3).

LF protects against iron dysregulation and oxidative stress in PD

Iron accumulation in the brain, a sign of brain dysfunction and neuro-metabolic disorder, is evident among PD patients (Mochizuki et al. 2020). Increased Fe^{3+} levels in substantia nigra of PD patients could trigger iron-mediated catalysis (Heber-Weiss reaction) that generate harmful free radicals and cause nerve cell degeneration. LF-binding receptors (LFRs) on neurons (perikarya, dendrites, axons), cerebral microvasculature, and glial cells in the mesencephalon contribute to iron metabolism in the brain. In PD patients, LFR density on neurons and micro-vessels is higher in the substantia nigra and show an increased nigral dopaminergic loss. This suggests that LFRs on vulnerable neurons may increase intraneuronal iron levels and contribute to the degeneration of nigral dopaminergic neurons in PD (Faucheux et al. 1995).

LF exists mainly in two metal-binding states: an iron-free 'apo' form and an iron-saturated 'holo' form. Other LF forms with partial Fe^{3+} saturation and other metal-bound states (i.e. Cu^{2+}, Mn^{2+}, CO^{2+}, Zn^{2+}) also exist in human physiology (Naidu 2000). Several studies have reported the neuroprotective benefits of LF forms against MPTP neurotoxicity in ventral mesencephalon neurons *in vitro* (Rousseau et al. 2013; Xu et al. 2019; Liu et al. 2020).

In the CNS, LF could prevent dopamine depletion in the striatum; as well as, iron deposition, oxidative and apoptotic processes in the substantia nigra. Also, LF downregulates the 'iron import protein – *divalent metal transporter1*', and up-regulate the 'iron export protein – *ferroportin1*'; while simultaneously reduce accumulation of nigral iron level. In the peripheral nervous system (PNS), LF alleviates increase in serum iron and ferritin; while decrease the serum total iron-binding capacity, loss of spleen weight, and reduce the spleen iron content. These neuroprotective effects could be a synergism between anti-iron dysregulation, antioxidative stress, and anti-apoptosis activities of LF (Liu et al. 2020).

LF prevents dopaminergic neurodegeneration and motor deficits in PD

LF is upregulated in DA-neurons resistant to degeneration in PD (Rousseau et al. 2013). The neuroprotective efficacy of LF is comparable to that of *glial cell line-derived neurotrophic factor*, a prototypical neurotrophic factor for DA-neurons. This neuroprotective effect is associated with the binding of LF to heparan sulfate proteoglycans located on the cell surface of DA-neurons that inactivate *focal adhesion kinase (FAK)*, a major effector kinase of integrins. Also, the iron-sequestration by LF could prevent iron-catalyzed oxidative stress and protect DA-neurons from apoptosis. Therefore, LF accumulation in PD brains could be considered a defense mechanism to avert the consequences of neurodegeneration (Rousseau et al. 2013). In the MPTP-induced murine PD model, LF showed improvement in PD-like motor dysfunction and prevented apoptosis of DA-neurons, neuroinflammation, and histological alterations (Xu et al. 2019).

LF-based delivery for PD interventions

Gene therapy is a promising pharmacological approach for clinical management of PD patients. Intravenous (i.v) administration of LF-modified nanoparticles loaded with *human glial cell line-derived neurotrophic factor* (hGDNF) could improve locomotor

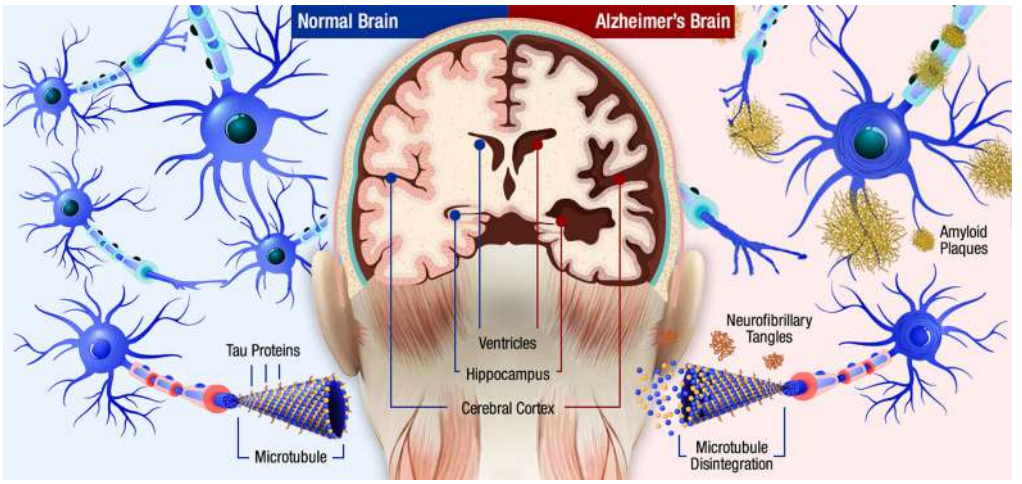

Figure 4. Alzheimer's Disease (AD) is a neurodegenerative condition results from accumulation of deformed senile β-amyloid plaques and neurofibrillary tangles of hyperphosphorylated tau proteins in the brain. AD is also associated with accumulation of iron (Fe^{3+}) or metal ions in the brain that cause oxidative stress. As an endogenous iron-chelator, LF is critical for clinical management of AD. LF could modulate the p-Akt/PTEN pathway and alleviate the pathological sequelae of AD (Mohamed *et al*. 2019).

activity, reduce DA-neuronal loss and enhance monoamine neurotransmitter levels in PD (Huang et al. 2009; 2010). Increased LF release by activated microglia results in elevated transmembrane redox potential of mitochondria, the suggested mode of action for neuroprotective effects of LF in PD (Wang et al. 2015). LF could also elicit iron-dependent neuroprotection by downregulation of TF receptors (Liu et al. 2020). Also, LF may upregulate *brain-derived neurotrophic factor* (BDNF) and activate the *regulated protein kinases-mitogen activated protein kinase* (ERK/MAPK) pathway. Accordingly, LF protects DA-neurons in the nigrostriatal area by decreasing levels of *α-synuclein* through upregulation of *hypoxia-inducible factor-1α* (HIF-1α) (Xu et al. 2019).

LF and Alzheimer's disease (AD)

Alzheimer's disease (AD) is a brain disorder characterized by dementia with severe problems in behavior, thinking and memory. This neurodegenerative condition is due to the accumulation of deformed β-amyloid (Aβ) and hyperphosphorylated tau proteins leading to formation and aggregation of senile plaques and neurofibrillary tangles in the brain. Furthermore, AD is associated with the accumulation of iron (Fe^{3+}) or metal ions in the brain that cause oxidative stress (Wang et al. 2019). During the aging process, iron may be deposited in different areas of the brain and cause impairment of normal cognitive function and behavior. Therefore, iron-targeted therapeutic strategies have emerged as a new hope in the clinical management of AD (Liu et al. 2018) (Figure 4).

LF in pathobiology of AD

LF is an endogenous iron chelator and a potent antioxidant in the brain to restore iron homeostasis. It also elicits anti-inflammatory activity and downregulates the levels of

TNF-α and IL-6. Human clinical studies showed a decrease in serum amyloid β, p-tau, and MAPK1 in AD patients (Mohamed et al. 2019). LF expression is upregulated in both neurons and glia in affected brain tissue of AD patients (Kawamata et al. 1993). In real-time PCR analysis, *LF-mRNA* expression in the cerebral cortex of AD patients was significantly greater than that in control group. Both reactive microglia in the cerebral cortex as well as monocytes and macrophages that infiltrate from circulation seem to be responsible for LF synthesis in the AD brain (An et al. 2009). LF upregulation in the cerebral cortex of AD patients could suggest a neuroprotective role for this iron-binding protein in AD-affected brain tissue (Wang et al. 2010).

LF as a diagnostic marker for early detection of AD

Current biomarkers for early detection of AD (i.e. CSF-tau and Aβ) levels are limited, invasive and expensive. Noninvasive biomarkers with required sensitivity and specificity could be a more practical, especially in screening of populations and identification of underdiagnosed subjects with early stages of 'mild cognitive impairment (MCI)' and AD (Carro et al. 2017). Low levels of salivary LF is prominent among patients with MCI and 'sporadic AD (sAD)'. Decline in salivary LF concentration could be due to downregulation of sAD associated systemic immunity (Bermejo-Pareja et al. 2020). Salivary LF, therefore, is considered a promising biomarker for (Aβ accumulation in AD) brain pathology (Olsen and Singhrao 2021). The clinical accuracy of salivary LF in the diagnosis of AD was compared with cerebral-Aβ load using amyloid-Positron-Emission Tomography (PET) neuroimaging (González-Sánchez et al. 2020). Salivary LF assay has excellent diagnostic correlation to differentiate the AD group from healthy controls. Also, salivary LF measurements could distinguish 'prodromal-AD' and 'AD-dementia' from 'frontotemporal dementia (FTD)' with over 87% sensitivity and 91% specificity. Salivary LF measurement serve as a novel, noninvasive and cost-effective biomarker assay in the diagnosis of AD.

LF in neuroprotection of AD

A major clinical feature of AD is linked to alterations in specific brain metabolic pathways. For example, deregulation of *phosphatidylinositol-4,5-bisphosphate 3-kinase (PI3K)/protein kinase B* (PKB or Akt) pathway could affect the inflammation and oxidative stress mediators in AD pathology. Oral LF supplementation (250 mg/day) of AD patients ($n = 50$) for 3 months could modulate the p-Akt/PTEN pathway and alleviate the pathological sequelae of AD (Mohamed et al. 2019). In human clinical studies, a decreased serum acetylcholine (ACh), serotonin (5-HT), antioxidant and anti-inflammatory markers, and a decreased expression of Akt in peripheral blood lymphocytes (PBL), as well as PI3K, and p-Akt levels in PBL lysate was observed in AD patients, which suggests a significant improvement. Similarly, elevated serum Aβ 42, cholesterol, oxidative stress markers, IL-6, heat shock protein (HSP) 90, caspase-3, and p-tau, as well as increased expression of tau, MAPK1 and PTEN in AD patients were significantly reduced. This study with AD surrogate markers provided a basis for a possible neuroprotective role for LF supplementation in alleviating the pathological cascade in AD and

cognitive decline in PD patients *via* modulation of the p-Akt/PTEN pathway (Mohamed et al. 2019).

Intranasal administration of human LF (2-6 mg/kg body wt) is shown to reduce Aβ deposition and ameliorated cognitive decline in AD. In an experimental AD mouse model, human LF facilitated non-amyloidogenic metabolism of *amyloid precursor protein* (APP) processing *via* activation of *α-secretase a-disintegrin and metalloprotease10* (ADAM10). The ADAM10 activation enhanced cleavage of the α-COOH-terminal fragment of APP and the corresponding elevation of the NH_2-terminal APP product, soluble APP-α (sAPPα) consequently reduced Aβ generation and improved the spatial cognitive learning ability in AD (Guo et al. 2017). In a recent study, oral supplementation of LF exerted neuroprotective effects in an *amyloid-β protein precursor transgenic* (AβPP-Tg) mouse model. Mice fed for 3 months with 2% LF-containing, 0.5% pepsin-hydrolyzed LF-containing (LF-*hyd*), and control diets were observed for memory impairment and AD pathogenesis. Both LF and LF-*hyd* diets elicited several neuroprotective benefits (Abdelhamid et al. 2020).

LF-based delivery for AD interventions

LF-based quercetin-encapsulated liposomes with RMP-7 (a bradykinin analog) showed reduction of Aβ-induced neurotoxicity and improved the viability of neurons *in situ* (Kuo and Tsao 2017). Also, the LF-based liposomes (compared to quercetin alone), significantly inhibit apoptosis of neuronal cells and elicit potent neuroprotective effects. In another study, LF conjugated with *polyamidoamine generation 3.0* (PAMAM G3.0) dendrimers effectively delivered rivastigmine (RIV) to the brain (Gothwal et al. 2018). Brain uptake of RIV was improved with LF-based conjugate by 4.2 and 8.0 times compared to PAMAM-RIV or RIV alone. Furthermore, the LF-based conjugate has significantly enhanced the overall locomotor activity with higher ambulation. Thus, LF-based drug conjugates show improved brain uptake and bioavailability with boosted memory in AD therapy. Galantamine (Gal), an approved drug for AD therapy, is limited by several side effects. A proteo-alkaloid conjugate of apo-LF + Gal could exert neuroprotection and neurotherapeutic benefits without side effects in AD therapy (Akilo et al. 2018). The apo-LF + Gal conjugate could prevent free radical generation, plaque formation, and iron accumulation in the brain. Natural amphiphilic micelles with LF and conjugated linoleic acid (CLA) show improved bioavailability and reduce brain oxidative stress, inflammation, apoptosis and acetylcholine esterase activity. The LF-CLA micelles also lower the Aβ peptide deposition; therefore, considered a potential target delivery system to reduce AD symptoms (Agwa et al. 2020).

LF and brain tumors

Cancer cells accumulate high levels of iron and ROS to promote their metabolic activity and growth. Ferroptosis is an oxidation-regulated cell death (apoptosis) driven by iron-dependent lipid peroxidation (Han et al. 2020). Dysregulation of mitochondrial metabolism is considered a biochemical feature of neurodegenerative diseases and various cancers (Seyfried 2015; Battaglia et al. 2020). Metabolic therapy with nutraceutical iron-chelators such as LF (Naidu 2000), could play a vital role in management of malignant

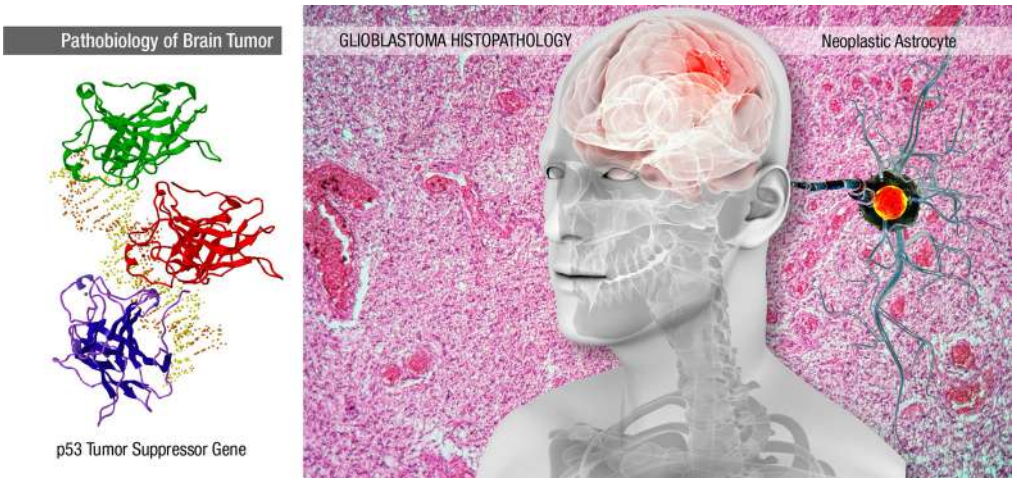

Figure 5. Glioblastoma is the most common and lethal type of brain cancer characterized by rapid growth, migration, and invasion of the surrounding parenchyma that leads to aggressive tumor metastasis. LF synthesized by neoplastic astrocytes, may regulate iron during cellular metabolism, prevent DNA damage and consequently tumorigenesis in the CNS. LF also elicits specific transactivation of the p53 tumor suppressor gene.

tumors by optimizing iron-dependent mitochondrial oxidative phosphorylation and ATP synthesis (Wallace et al. 2019). Besides its regulatory role in iron homeostasis with its metal-binding/transport, and Fe^{3+} sequestration properties, LF also elicits potent anti-tumor activity. LF is cytotoxic against several cancers in distinct ways under different conditions with effects such as cell membrane disruption, cell cycle arrest, cell immunoreaction and induction of apoptosis (Zhang et al. 2014; Cutone et al. 2020). The ability of LF to deregulate apoptosis has major clinical implications in evading drug resistance and radio-resistance in cancer therapy (Kanwar and Kanwar 2013). In nanomedicine, LF has currently emerged as an ideal carrier for target delivery of chemotherapeutic drugs. The ability of LF to cross the BBB, makes this innate transport system an effective module in prevention and treatment of brain tumors, especially in combination therapies.

Antitumor effects of LF against glioblastoma

Glioblastoma is the most common and lethal type of brain cancer characterized by rapid growth, migration, and invasion of the surrounding parenchyma that leads to aggressive tumor metastasis. The presence of LF in astrocytomas, anaplastic astrocytomas and multiforme glioblastomas was reported (Tuccari et al. 1999). LF synthesis by neoplastic astrocytes seems to regulate iron during cellular metabolism. LF may exert an anti-inflammatory function *via* its inhibitory effect on free radical formation; thereby, prevent DNA damage and consequently tumorigenesis in the CNS. LF could also elicit specific transactivation of the p53 tumor suppressor gene (Sacharczuk et al. 2005) (Figure 5).

Since BBB restricts transport of most antitumor drugs, regular chemotherapy has limited efficacy to eradicate brain glioma cells. Human LF could inhibit human

glioblastoma cell growth by the downregulation of cyclin D1 and D4. LF administration (60 mg/kg/day in nude mice) decreased tumor size by ~30%. In combination chemotherapy with temozolomide, LF showed a synergistic effect both *in vitro* and *in vivo* (Arcella et al. 2015). LF-modified daunorubicin combined with honokiol liposomes could activate apoptotic enzyme *caspase three* and down-regulate *vasculogenic mimicry protein indicators* (PI3K, MMP-2, MMP-9, VE-Cadherin and FAK) in brain glioma cells. LF-modified liposomes improve accumulation of chemotherapeutic drug in brain glioma tissue and improve efficacy of antitumor therapy (Liu et al. 2017).

Neuroblastoma cells treated with apo- and iron-saturated bLF resulted in neuronal differentiation and expression of specific differentiation markers, *β-tubulin III* and *neurofilaments*. These bLF treatments downregulate endogenous *survivin*, responsible for cell proliferation; as well as, *miRNA 584* and *miRNA214-3p*, required for cell differentiation (Sriramoju et al. 2015). Based on iron-saturation status, holo-LF partially or totally inhibits the migration of human glioblastoma cells. At molecular level, LF downregulates both SNAIL and *vimentin* expression, while inducing a notable increase in cadherin levels and inhibiting IL-6/STAT3 axis (Cutone et al. 2020).

LF-based delivery of chemotherapeutics for brain tumors

About 97% of nanoparticles (NP) could enter the tumor site *via* an active trans-endothelial transport as shown in glioblastoma xenograft model (Sindhwani et al. 2020). A nano-emulsion of LF-targeted huperzine A showed increased accumulation in brain cells *via* transcytosis compared to untargeted NP-emulsion (Meng et al. 2018). Similar, transcytosol delivery of LF-temozolamide-NP-drug to brain tumor site was also reported (Kumari et al. 2017). LF-modified procationic liposomes loaded with chemotherapeutic agents (doxorubicin and tetrandrine) could effectively translocate into glioma C6 cells *via* receptor- and adsorption-mediated endocytosis. LF-conjugation increase transcytosis and improve survival rates of animals inoculated with C6 glioma cells compared to the control group (Chen et al. 2011). LF-NP loaded with *Aurora Kinase B (AKB) siRNA* demonstrate enhanced chemotherapeutic efficiency of temozolomide against glioblastoma multiforme (GBM) (Kumari et al. 2018). Over expression of AKB in malignant glioma is known to induce degradation of *tumor suppressor gene p53* that triggers tumor growth. The combination therapy with temozolomide + AKB/LF-nanocarriers significantly improve survival rates (from 14 to 33 days). Intranasal uptake of LF-modified conjugates increase brain accumulation due to high density of LF receptors on the BCEC surface (Pandey et al. 2019). Taken together, LF-conjugates demonstrate improved cellular uptake of therapeutics compared to their unmodified counterparts. Besides drug delivery, the cationic nature of LF enables both high-affinity binding to nucleic acids and potentiates endosomal activity.

LF effects on sleep-wake cycle

Sleep is a neurochemical process that supports critical brain functions and facilitates memory consolidation. Sleep deprivation is a comorbidity for many psychiatric disorders including major depressive disorder (MDD), anxiety, post-traumatic stress disorder (PTSD), and drug addiction. The suprachiasmatic nucleus (SCN), a small group of

hypothalamic nerve cells in the brain, functions as a master circadian pacemaker to control the timing of sleep-wake cycle and coordinates the circadian rhythm (Moore 2007). An endogenous circadian rhythm in the BBB controls the transporter function and regulates permeability across the BBB. Furthermore, sleep supports clearance of waste metabolites and promotes endocytosis across the BBB (Cuddapah et al. 2019).

Poor sleep can lead to restless leg syndrome, autonomic disorders, fatigue and many brain disorders. Excess iron deposition in the brain is a major causative factor for neuroinflammation from activated microglia and neurotoxicity from targeted neurons. LF could inhibit both iron deposition-related neuroinflammation as well as neurotoxicity and improve the sleep architecture (Yu et al. 2013). Severe or chronic stress is associated with negative health outcomes including disruptive sleep/wake cycles. A diet containing LF, prebiotics, and milk fat globule membrane is shown to enhance sleep quality and lower the impact of stress on sleep and diurnal rhythms (Thompson et al. 2017). A randomized controlled trial of healthy Japanese children ($n = 109$) between the ages of 12 and 32 months found consumption of LF (48 mg/day)-fortified formula compared to placebo resulted in a significant improvement in sleep parameters and alleviated the complications of restless leg syndrome (Miyakawa et al. 2020).

Melatonin, the nocturnal hormone synthesized by the pineal gland, serves as a time cue and sleep-anticipating signal. An interaction exists between melatonin, the sleep-wake cycle, core temperature, blood pressure, immune and hormonal rhythms, in the optimization of internal temporal order. LF acts in synergy with melatonin to prevent peroxidation of polyunsaturated fatty acids, and oxidation of the amino acid phenylalanine. The LF-melatonin synergy may have the potential to relieve oxidative stress and protect from neuronal damage (Falsaperla et al. 2020).

LF for stress management

Stress has long been known to induce an immune response. Interaction between the CNS and the immune system is achieved *via* the hypothalamus-pituitary-adrenal (HPA) and sympathetic-adrenal medullary (SAM) axes. Effective regulation of HPA and SAM axes and their functional receptors could help alleviate the potentially harmful effects of stress on immune function. Oral administration of LF could reverse stress-induced changes in the humoral and cellular immune responses (Zimecki and Artym 2004).

Bovine milk LF could prevent distress induced by maternal separation *via* an opioid-mediated mechanism (Takeuchi et al. 2003). LF also exerts analgesia *via* a mu-opioid receptor-mediated response in the spinal cord. Bovine LF acts as an enhancer of spinal opioidergic system *via* nitric oxide (NO·)-mediated mechanism (Hayashida et al. 2003). LF is shown to prevent the tolerance to morphine-induced analgesia *via* selective activation of neuronal nitric oxide synthase (nNOS) (Hayashida et al. 2004). LF-mediated selective activation of nNOS accelerates NO· production and this nociceptive effect of LF could enhance the endogenous opioid system *via* cyclic guanosine monophosphate (GMP) production (Tsuchiya et al. 2006).

LF may prevent immune compromised state induced from psychosocial stress *via* an opioid-mediated mechanism (Sacharczuk et al. 2005). Thus, LF may suppress psychological distress, especially during moderate stress conditions. Intraperitoneal (i.p)

injection of bovine LF (100 mg/kg) could reduce stress behaviors which is reversed by pretreatment with naloxone, an opioid receptor antagonist (Kamemori et al. 2004). LF acts as an adaptogen during experimental stress and ameliorates stress-induced surge in corticosterone levels within 30 min. Also, LF normalizes stress-induced changes in neutrophils within 30 min in blood and 3 h after exposure to stress (Aleshina et al. 2016).

An anti-depressant-like effect for LF was reported in a murine 'repeat forced-swim test' (FST). Bovine LF supplementation is shown to improve the depressive-like symptoms induced by repeated FST challenge (Takeuchi et al. 2017). Ovariectomy (OVX) in rats has been shown to suppress decreased locomotor function by improving dopamine and serotonin release in the amygdala (Izumo et al. 2012).

LF and *Neuro*-COVID-19

Coronavirus disease-2019 (COVID-19) since its initial emergence in Wuhan, China, has been considered mostly a respiratory illness; however, the virulence spectrum of *Severe Acute Respiratory Syndrome Coronavirus-2* (SARS-CoV-2) to cross the BBB and inflict a plethora of neuropathological manifestations in the CNS has turned the current pandemic into a major mental illness – the *Neuro*-COVID-19. Aside from systemic and respiratory ailments, 36.4% of *Neuro*-COVID-19 patients develop neurological symptoms (Mao et al. 2020), which in some cases are prominent and others only manifestations (Bai et al. 2020). Neuropathology and cognitive health complications; however, are high among patients with severe COVID-19 infection (Yachou et al. 2020). Headache is the most common CNS sign in *Neuro*-COVID-19 patients with prevalence varying from 6.5 to 23% and confusion or impaired consciousness among 9.0% of cases (Niazkar et al. 2020).

Common neurological symptoms in *Neuro*-COVID-19 patients include headache, dizziness, myalgia, and complications such as encephalitis, encephalopathy, stroke, and epileptic seizures (Acharya et al. 2020). The peripheral nervous system (PNS)-related manifestations include hyposmia/anosmia (smell disorder), hypogeusia/dysgeusia (taste disorder), rhabdomyolysis, and Guillain-Barre syndrome (Carod-Artal 2020; Montalvan et al. 2020). Smell and taste disorders are frequent PNS manifestations that suddenly appear with mild symptoms of nasal obstruction or excessive nasal secretion (Vaira et al. 2020). The incidence of olfactory dysfunction may vary from 34 to 68%, mostly among female patients (Meng et al. 2020). Neuropathological symptoms at times appear to precede typical clinical signs like fever and cough. These signs are also widespread among asymptomatic individuals or as the initial presentation of COVID-19 with no other clinical manifestations (Gane et al. 2020). Such asymptomatic carriage should be considered a potential threat for rapid transmission of COVID-19 infection in the community.

Microglial-LF and anti-viral effects

Neuroglial cells, such as astrocytes and microglia, are vital for CNS response against microbial and toxic insults. Neuroglial dysfunction also leads to neuroinflammatory condition; therefore, these brain cells are primary target for SARS-CoV-2 (Vargas et al. 2020). As an integral part of brain's glymphatic and innate immune system, the cytokine

secretion by astrocytes and microglia influence the clinical outcomes of encephalitic coronavirus infection. Accordingly, microglial-derived defense factors play a major role in protecting the brain from *Neuro*-COVID-19 infection. Furthermore, microglia modulate the CNS micro-milieu, thereby reduce the severity of demyelination, and influence neuronal repair in cerebral cortex (Lavi and Cong 2020; Tremblay et al. 2020).

During a viral infection of the CNS, resident macrophages in the brain – the microglia, activate from dormancy to secrete various proinflammatory mediators, immune modulators and defense factors including LF. This endogenous iron-binding protein is involved in the regulation of redox signaling pathways that scavenge free radicals, oxidative stress and various pro-inflammatory cytokines (Legrand et al. 2005; Campione et al. 2020). At cellular level, LF modulates the antigen-presenting cell (APC) cascade, including cellular migration and activation; whereas at molecular level, LF affects expression of soluble immune mediators, i.e. cytokines, chemokines and other effector molecules that regulate inflammatory and immune responses (Siqueiros-Cendón et al. 2014). LF exerts antiviral effects against a broad range of viruses, including SARS-CoV, a pathogen closely related to the SARS-CoV-2 (Berlutti et al. 2011; Lang et al. 2011; Wakabayashi et al. 2014). These multifunctional activities, combined with redox-based control of oxidative stress, makes LF a potential host defense factor to combat cytokine release syndrome ('cytokine storm') and acute inflammation-related pathologies typical for *Neuro*-COVID-19 (Chang et al. 2020; Naidu et al. 2020b).

SARS-CoV-2 transmission and entry into brain

SARS-CoV-2 could infect the brain through neuroaxonal and hematogenous modes of transmission. The neuroaxonal transmission includes nasal (olfactory nerve track), ocular (optic nerve tract), and gastrointestinal (vagus nerve track) routes by trans-synaptic transfer *via* brain stem (Jakhmola et al. 2020). The hematogenous transmission is mainly through the pulmonary/circulatory routes *via* the BBB. Receptor recognition is the first step of viral infection, a key determinant of host cell/tissue tropism. Coronaviruses have evolved several complex host cell surface receptor recognition patterns. Angiotensin-converting enzyme 2 (ACE2) is a potential receptor for SARS-CoV-2 cellular docking and entry (Hoffmann et al. 2020), and ACE2 is widely expressed on various brain cells and cerebral regions. The resident CNS cells such as astrocytes and microglia also express ACE2; thereby, provide potential docking sites for viral attachment/entry into the brain (Jakhmola et al. 2020). A recent study reported that *neuropilin-1* (NRP1), known to bind furin-cleaved substrates, could potentiate SARS-CoV-2 infection (Cantuti-Castelvetri et al. 2020). NRP1 is abundantly expressed in the respiratory and olfactory mucosa, with highest expression in endothelial and epithelial cells. Furthermore, SARS-CoV-2 also recognizes four other putative receptors on host cells; and binds to proteoglycans such as heparan sulfate *via* lectin-type interactions. Versatility in cell surface receptor interactions makes SARS-CoV-2 a multi-tropic viral pathogen (Naidu et al. 2020a).

LF as a viral adhesion blocking agent

LF is a potent microbial adhesion blocking agent and prevents attachment of pathogens to host mucosa (Naidu et al. 2004). Also, LF could block viral entry into the host cell,

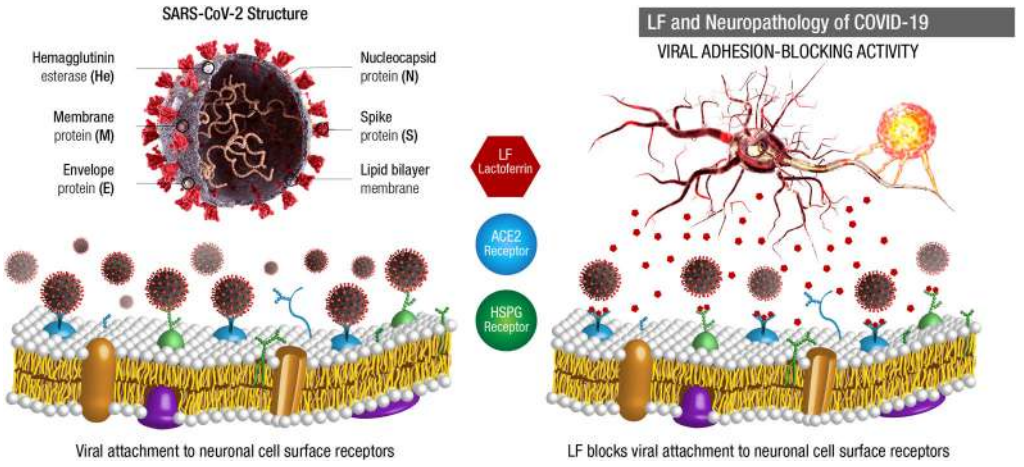

Figure 6. Coronaviruses have evolved several complex host cell surface receptor recognition patterns. Angiotensin-converting enzyme-2 (ACE2), widely expressed on various brain cells and cerebral regions, is a potential receptor for SARS-CoV-2 cellular docking and entry. SARS-CoV-2 also recognizes four other putative receptors on host cells; and binds to proteoglycans such as heparan sulfate *via* lectin-type interactions. Versatility in cell surface receptor interactions makes SARS-CoV-2 a multi-tropic viral pathogen (Naidu *et al.* 2020a). LF could block viral entry into the host cell, either by binding to cellular receptors, or by direct interaction with the virus particle.

either by binding to cellular receptors, or by direct interaction with the virus particle. Heparan sulfate proteoglycans (HSPGs) serve as initial adhesion targets for several viruses and LF could block viral entry by competitive binding to HSPGs and interfere with the early phase of viral pathogenesis (Andersen et al. 2004; Pietrantoni et al. 2015). Several studies have demonstrated LF-mediated blocking of CoV attachment to host cell surface HSPGs in murine coronavirus, human coronavirus (CoV-NL63), and pseudotyped SARS-CoV (de Haan et al. 2005; Lang et al. 2011; Milewska et al. 2014) (Figure 6).

An LF-derived peptide (*LRPVAA*) has been shown to block ACE receptor activity *in vitro* (Lee et al. 2006). Furthermore, a LF hydrolysate and its derived peptides could block binding to ACE receptors and thus inhibit angiotensin (ANG) II-induced vasoconstriction (Fernández-Musoles et al. 2014). The nuclear localization of LF in different human epithelia allows this iron-binding protein to inhibit intracellular replication of viruses through induction of antiviral cytokines such as interferon (IFN)-α/β. LF administration also enhance natural killer (NK) cell activity and T_H1 cytokine response, which protects against viral infections (Berlutti et al. 2011; Wakabayashi et al. 2014). Taken together, LF released from activated microglia may protect the CNS from SARS-CoV-2 infection by blocking viral attachment to the cell membrane; thus, limiting the neuronal entry of the virus; intracellular inhibition of viral replication, and modulation of systemic immune response (Naidu et al. 2020b).

Hypoxia-induced CNS pathology during Neuro-COVID-19

SARS-CoV-2 binding to ACE2 receptors on brain capillary endothelia may disrupt the BBB and facilitate viral entry into the CNS. SARS-CoV-2 infection of brainstem neurons

may disrupt cardio-respiratory regulation and cause severe pneumonia, and hypoxia-mediated brain damage (Steardo et al. 2020). Secondary mechanisms involve hypoxia (due to respiratory failure); as well as, various forms of encephalopathy, white matter damage, and abnormal blood clotting that may result in stroke. Cerebral microhemorrhage due to hypoxia has been recognized as a severe complication in *Neuro*-COVID-19, which triggers neuronal swelling, brain edema and damage to the CNS (Jaunmuktane et al. 2020). Oxygen levels play an essential role in cellular metabolism and O_2 fluctuations are known to regulate the expression of several proteins, including *hypoxia-inducible factor (HIF)*, the redox-sensitive transcription factor (Wang et al. 1995). Hypoxia lowers the terminal electron acceptor (O_2) and increases the oxidative stress within a cell due to insufficient terminal electron acceptors, a prerequisite for oxidative phosphorylation. Stabilization of HIF is critical for survival of neurons during hypoxia. Accordingly, the stabilized HIF upregulates aerobic glycolysis to generate ATP to meet the metabolic energy demand (Semenza 2000).

Human apo (iron-free)-LF is shown to stabilize both HIF-1α and HIF-2α, while providing neuroprotection against hypoxia-induced brain damage (Zakharova et al. 2018). Holo (iron-saturated)-LF could catalyze the conversion of hydrogen peroxide (H_2O_2) to oxygen and alleviate hypoxic microenvironment in tumor pathology (Zhang et al. 2019). LF has also been shown to counteract hypoxia-induced alterations in the cortical tissue and facilitated repair of damaged microstructures in the white matter (van de Looij et al. 2014). In injured or hypoxic tissue, such as SARS-CoV-2 infected CNS, treatment with hyperbaric oxygen might prove useful in increasing tissue oxygenation and thereby restoring the innate host defense (Bullen et al. 2006); which is a huge recovery advantage for COVID-19 patients. However, reoxygenation could increase the risk of tissue damage after severe hypoxia. As an endogenous iron-chelator in the cytosol, LF could effectively minimize the reoxygenation-associated risks (Shimmura et al. 1998).

Immune-mediated brain injury during Neuro-COVID-19

The hallmark of COVID-19 pathogenesis is the cytokine storm, resulting from activated monocytes/macrophages, dendritic cells, T-cells, mast cells, and neutrophils. During cytokine storm, some cytokines could cross the BBB and activate immune cells of the brain to release neuronal cytokines (Jakhmola et al. 2020). In the CNS, the activation of resident immune cells including microglia and astrocytes may lead to chronic immune imbalance, which may cause synaptic changes and neuropsychiatric impairments.

Both immunomodulatory as well as anti-inflammatory effects of LF could positively influence host responses to COVID-19 infections (Naidu et al. 2020b). Anti-inflammatory activities of LF are based on the protein's ability to enter host cells through receptor-mediated endocytosis and regulate pro-inflammatory gene expression (Suzuki et al. 2008). LF downregulates pro-inflammatory cytokines and potentiates adaptive immune response (Frioni et al. 2014). LF also modulates antigen-specific adaptive immune responses (i.e. APC activation, maturation, migration, and antigen presentation) and bridges the functions of both T- and B-cells (Legrand et al. 1997). Structural changes in

the N-terminal 'basic' domain of LF facilitates its molecular interactions with B lymphocytes (Padhan et al. 2008).

Neuropathological comorbidities in neuro-COVID-19

COVID-19 infection may aggravate the clinical spectrum of neuropathological comorbidities. The presence of coronavirus is reported in the brain tissue of patients with PD and AD and multiple sclerosis (MS) (Matías-Guiu et al. 2020). The multifunctional neuroprotective benefits of LF has been attributed to: i) suppression of iron-catalyzed hypoxia and oxidative stress, ii) prevention of cellular apoptosis and neurodegeneration, iii) activation of antioxidant enzymes and removal of free radicals and related reactive oxygen and nitrogen species to maintain redox homeostasis in the CNS milieu.

LF for neuro-COVID-19 comorbidity with PD

SARS-CoV-2 enters the brain through olfactory bulb and causes anosmia/hyposmia (Antonini et al. 2020). Interestingly, hyposmia is a common premotor clinical condition in PD, involved in α-*synuclein* pathology (Braak et al. 2003). COVID-19 may worsen both motor and non-motor symptoms in PD causing severe complications on the quality of the life and mental health (Ferini-Strambi and Salsone 2021). The impact of COVID-19 on PD patients, however, cannot be restricted only to motor symptoms. ACE2 receptors are widespread in the cardio-respiratory centers in the medulla, DA-neurons of striatum and substantia nigra (Rodriguez-Perez et al. 2020). This makes the brain cortex highly vulnerable to SARS-CoV-2 infection. Coincidentally, the same brain regions are also associated with most neurodegenerative diseases (Gomez-Pinedo et al. 2020); therefore, COVID-19 might trigger neuronal damage in PD and accelerate aging in brain tissues.

LF inhibits iron-catalyzed oxidative stress, protects the DA-neurons from apoptosis, averts neuroinflammation, and substantially ameliorates PD-like motor dysfunction (Rousseau et al. 2013). In PD patients, LF prevents excessive iron accumulation, upregulates *divalent metal transporter* (DMT1) and TF receptor (the main intracellular iron regulatory protein), and subsequently improves the activity of several redox enzymes. The neuroprotective effects of LF also involve upregulation of *brain-derived neurotrophic factor* (BDNF), and *hypoxia-inducible factor 1α* (HIF-1α) (Xu et al. 2019). These findings suggest that LF may play an important role in ameliorating PD-associated brain abnormalities and movement disorders amplified during COVID-19.

LF for neuro-COVID-19 comorbidity with AD

The geriatric population is at higher risk for mortality due to SARS-CoV-2 infection with the case fatality rate (CFR) in patients aged above 80 years is >20% (Covino et al. 2020). Severe outcomes of *Neuro*-COVID-19 is often associated with 'cytokine storm', a severe inflammatory response that could trigger amyloid-stimulated neuropathology in AD patients (Naughton et al. 2020). COVID-19 positive pre-symptomatic individuals with undiagnosed AD, show accelerated clinical manifestations, especially neuropsychiatric signs. In addition, affected patients could be at higher risk of developing cognitive

decline after overcoming the primary COVID-19 infection (Ferini-Strambi and Salsone 2021). Human LF could reduce Aβ deposition and ameliorate cognitive decline in AD (Guo et al. 2017). Oral supplementation of LF showed neuroprotective benefits in AD pathology, which include reduction of Aβ levels and enhanced degradation of Aβ in the brain (Abdelhamid et al. 2020). These multifunctional benefits make LF a potent neuroprotective agent for treatment and/or prevention of AD comorbidities.

Conclusions

This narrative review elucidates the potential role of LF-derived from activated microglia in several neurological pathways of CNS and brain physiology. It also depicts the consequences of LF deficiency or dysfunction about the development of neuropathologies (i.e. iron imbalance, oxidative stress, hypoxia, amyloid plaque formation, and degeneration of DA-neurons) that comprise typical symptoms of PD, AD, brain tumors, and other brain disorders. Several studies are cited to elaborate on the neuroprotective benefits of LF including: i) immune-modulatory effects to resolve inflammatory responses; ii) neuro-redox regulation to ameliorate oxidative stress and hypoxia; iii) broad antiviral activity with direct and indirect effects on host-pathogen interactions; iv) effective transport of drugs and bioactives across the intestinal lining and BBB; and v) support effective sleep architecture and stress management.

Based on previous coronavirus outbreaks (i.e. SARS and MERS), there is serious concern that COVID-19 survivors are at higher risk in developing neurodegenerative disorders years or decades later (Rogers et al. 2020). Patients develop transient delirium (with and without hypoxia) after COVID-19 infection as well as other neurological manifestations (Lim et al. 2020). In a recent cohort study ($n = 402$), a significant proportion of COVID-19 patients self-rated in the psychopathological category: 28% for post-traumatic stress disorder (PTSD), 31% for depression, 42% for anxiety, 20% for obsessive compulsive (OC) symptoms, and 40% for insomnia (Mazza et al. 2020). Therefore, affected patients may be at higher risk for developing cognitive decline after overcoming the primary COVID-19 infection (Heneka et al. 2020). Prospective monitoring of COVID-19 patients for cognitive health is vital to develop effective clinical nutrition and dietary supplement protocols for recovery, rehabilitation, and quality healthcare. Several human clinical studies are underway to establish the potential health benefits of LF supplementation for management of mental health comorbidities during COVID-19 pandemic.

Disclosure statement

The authors SAGN and ASN are affiliated with N-terminus Research Laboratory. The authors TCW and KJAD have no potential conflict of interest to disclose.

Dedication

Clyde F. Wallace, Jr, born June 9th, 1949 in Hopkinsville Kentucky passed on December 2nd, 2020 due to a COVID-19 infection that occurring amongst his fight with Parkinson's disease. He was a natural born teacher and mentor who dedicated his life's work to local community

education, particularly among those underserved children in Christian County, Kentucky. In 1987 the Governor of Kentucky conferred upon him the status of Colonel, the highest title of honor bestowed by the Commonwealth of Kentucky, for his contributions and outstanding service to advancing education in the state. Wallace is survived by his son, Dr. Taylor C. Wallace.

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