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Review Article

Alzheimer's Disease and COVID-19 Pathogenic Overlap: Implications for Drug Repurposing

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ABSTRACT: As COVID-19 continues, a safe, cost-effective treatment strategy demands continued inquiry. Chronic neuroinflammatory disorders may appear to be of little relevance in this regard; often indolent and progressive disorders characterized by neuroinflammation (such as Alzheimer's disease (AD)) are fundamentally dissimilar in etiology and symptomology to COVID-19's rapid infectivity and pathology. However, the two disorders share extensive pathognomonic features, including at membrane, cytoplasmic, and extracellular levels, culminating in analogous immunogenic destruction of their respective organ parenchyma. We hypothesize that these mechanistic similarities may extent to therapeutic targets, namely that it is conceivable an agent against AD's immunopathy may have efficacy against COVID-19 and vice versa. It is notable that while extensively investigated, no agent has yet demonstrated significant therapeutic efficacy against AD's cognitive and memory declines. Yet this very failure has driven the development of numerous agents with strong mechanistic potential and clinical characteristics. Having already approved for clinical trials, these agents may be an expedient starting point in the urgent search for an effective COVID-19 therapy. Herein, we review the overlapping Alzheimer's/ COVID-19 targets and theorize several initial platforms.

RÉSUMÉ : La maladie d'Alzheimer et le chevauchement pathogène de la COVID-19 : implications pour le repositionnement des médicaments employés. Alors que la pandémie de COVID-19 se poursuit, une stratégie de traitement sécuritaire et efficace par rapport au coût exige des efforts continus en recherche. À cet égard, les troubles neuro-inflammatoires chroniques peuvent sembler peu pertinents. Souvent indolents et progressifs, les troubles caractérisés par une neuro-inflammation, par exemple la maladie d'Alzheimer, sont fondamentalement différents, dans leur étiologie et leur symptomatologie, de l'infectiosité rapide et de la pathologie de la COVID-19. Cependant, ces deux maladies partagent des caractéristiques pathognomoniques étendues, y compris aux niveaux membranaire, cytoplasmique et extracellulaire, qui aboutissent à une destruction immunogène analogue du parenchyme de leurs organes respectifs. Nous émettons donc l'hypothèse que ces similitudes mécanistiques peuvent s'étendre à des cibles thérapeutiques, à savoir qu'il est concevable qu'un agent contre l'immunopathie de la maladie d'Alzheimer puisse être efficace contre une infection à la COVID-19 et vice-versa. Malgré des recherches approfondies en la matière, il est à noter qu'aucun agent n'a encore fait preuve d'une efficacité thérapeutique notable contre le déclin des fonctions cognitives et de la mémoire dans le cas de la maladie d'Alzheimer. C'est pourtant cet échec qui a conduit au développement de nombreux agents dotés d'un fort potentiel mécanistique et de caractéristiques cliniques. Ayant déjà été approuvés pour des essais cliniques, ces agents peuvent constituer un point de départ avantageux dans la recherche urgente d'une thérapie efficace contre les infections à la COVID-19. En somme, nous voulons ici passer en revue les cibles de la maladie d'Alzheimer et de la COVID-19 qui se recoupent et théoriser, pour ce faire, plusieurs avenues initiales de recherche.

Keywords: Alzheimer's disease; COVID-19; Neuroinflammation; Neuroimmune; Drug repurposing

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Introduction

COVID-19 has emerged as the defining pandemic of our age. As resurgent outbreaks continue to escalate prevalence and mortality, and public patience for restrictive social health measures wanes, the search for an effective therapy demands ongoing urgency.[1,2]

Currently, there are multiple strategies under continuing exploration for the development of treatments, which include re-evaluation of prior coronavirus (SARS and MERS) therapies;[3,4] development of novel antivirals, as well as adjunctive innovations in testing and prophylaxis/vaccination. All are worthwhile and necessary avenues of inquiry; yet an additional, and frequently disregarded, area of research

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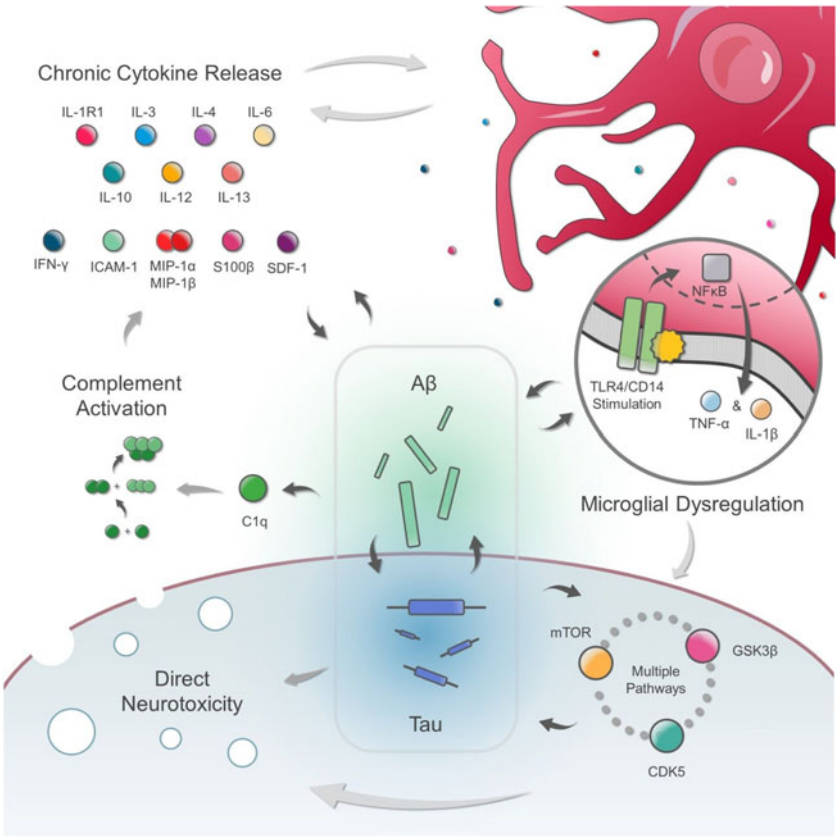

Figure 1: Alzheimer's immunopathy. Multiple concurrent immunopathies are described in AD. These include complement activation via factor C1q, a pro-inflammatory cytokine cascade (involving IL-1R1, IL-3, IL-4, IL-6, IL-10, IL-12, IL-13, IFN-γ, ICAM-1, MIP-1α/MIP-1β, S100β, and SDF-1); microglial dysregulation – mediated by TLR4 and CD14 stimulation causing additional pro-inflammatory cytokine release (TNF-α and IL-1β); mTOR/GSK3β/CDK5 pathway activation. These reciprocally interact with Aβ and tau proteopathies, likely in synergism, and contribute to neurotoxicity and cell death.

is the repurposing of existing therapeutics among disorders sharing etiological and pathological overlap with COVID-19. Like Alzheimer's disease (AD), COVID-19 is a global disease, demanding cost-effective, available global solutions – drug repurposing is one avenue to such solutions.

Disorders of neuroimmunology, such as AD, may appear to show little relevance to therapy development for COVID-19. As a progressive disorder of neurodegeneration, marked by gradual declines of memory, cognition, and executive function, AD bears remarkably little in common to a rapid viral infection of the lung and other organs. However, both diseases share an immunogenic destruction of their respective organ parenchyma which bears substantial mechanistic overlap. As we briefly outline in this perspective, this destruction may also derive from similar cellular and signaling pathways. Moreover, with a propensity for COVID-19 to induce severe disease among the elderly, the diseases also share a common risk pool.

Herein, we present an argument that this pathological overlap may be a viable, and yet unexplored, therapeutic avenue. Namely, that therapies developed for Alzheimer's immunopathy may have utility against COVID-19. It is notable that currently no small molecule disease-modifying therapies against AD exist. However, the very lack of a therapy has driven hundreds of clinical trials over the past decades, affording a wide body of work – well evidenced and rigorously assessed. Nonetheless, only a small number of those trials have been positive, namely the β-amyloid (Aβ)-targeting monoclonal antibodies, donanemab and lecanemab.[5,6] Furthermore, treatments against COVID-19 need not contend with the blood–brain barrier, abstract variables such as memory or cognition, or arresting disease processes which have preceded the treatment by years, if not decades. It is therefore possible that with sound mechanistic justification, a treatment candidate for COVID-19 could be discerned from AD research. It is also conceivable that in years to come, therapeutics devised for the COVID-19 pandemic may have some utility in the development of a treatment for the AD pandemic.

Mechanistic Similarities between AD and COVID-19

AD and Its Immunopathy

AD is characterized by cytotoxic immuno-inflammation synergised with concomitant neurotoxic protein misfolding of Aβ and tau, culminating in parallel, interconnected proteopathic and immunopathic pathogeneses (see Figure 1).[7]

The precise etiology of these events remains intensely controversial with neither the proteopathies nor the immunopathies definitively shown to precede the other; however, it is established that once aggregated, AD's proteopathies can recruit an expanded innate immune response involving a complement cascade (initiated by C1q); the production of inflammatory cytokines (interleukins [IL], interferons [IFN]); and elevation of inflammation-associated peptides: IL-1R1, IL-3, IL-4, IL-6, IL-10, IL-12, IL-13, IFN-γ, intracellular adhesion molecule 1 (ICAM-1), macrophage inflammatory proteins (MIP-1α/MIP-1β), S100 calcium-binding protein B (S100β), and stromal cell-derived factor 1 (SDF-1).[8]

This hyper-inflammatory state can further promote localized microglia-mediated dysregulation of innate immunity,

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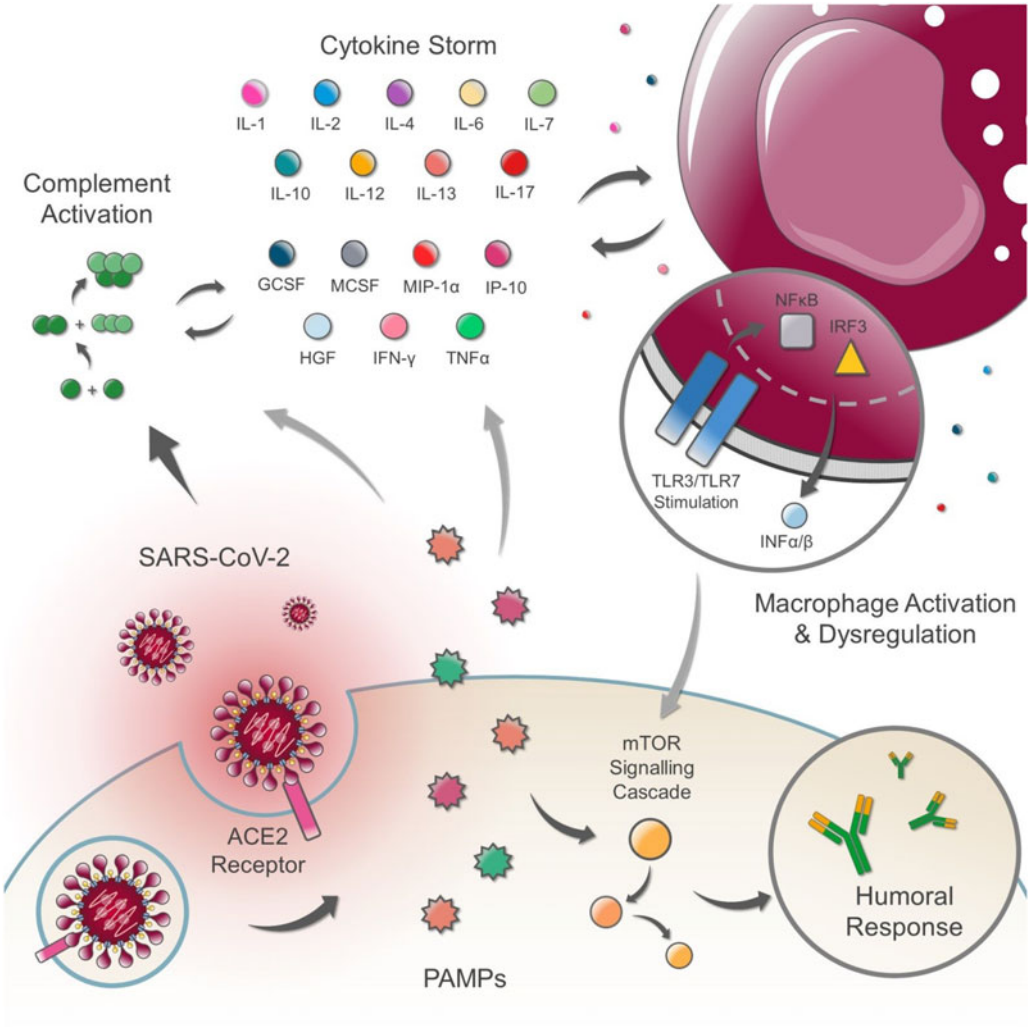

Figure 2: COVID-19 immunopathy. Upon adhesion and infection of cells, COVID-19 induces cytological damage, culminating in the release of PAMPs. These signals, in turn with immunogenic reactions to the virion itself, lead to activation of complement, concomitant with a pro-inflammatory cytokine storm (involving IL-1, IL-2, IL-4, IL-6, IL-7, IL-10, IL-12, IL-13, IL-17, GCSF, MCSF, IP-10, MCP-1, MIP-1 α, HGF, IFN-γ, and TNF-α). Cumulatively, these promote macrophage activation and dysregulation via the TLR3/TLR7 receptors, mediating additional cytokine release. This can be accompanied by mTOR signaling with modulates the humoral response against the infection.

co-operatively augmenting ongoing proteopathic–immunopathic neurotoxicities. Converse activation of other cellular pathways, including mammalian target of rapamycin (mTOR), glycogen synthase kinase 3 beta (GSK3β), and cyclin dependent kinase-5 (Cdk5) kinases, can reciprocally augment neurotoxicities and inhibit neuroprotective mechanisms such as autophagy. These pathological processes afford multiple druggable targets against AD's combined proteopathic–-immunopathic assault. Other cellular targets, including membrane lipids (especially cholesterol), mitochondria, endoplasmic reticulum (ER), and synapses, also provide complementary druggable targets within the pathogenic cascade of AD.

COVID-19 and Its Immunopathy

COVID-19 is typically the manifestation of SARS-CoV-2 viral pneumonia. It arises both from infective destruction of local lung parenchyma and principally from cytotoxic immuno-inflammation induced by dysregulated activation of lung and systemic immune elements. This culminates in parallel, interconnected viral and immunopathic pathogeneses (See Figure 2).

Viral pathology commences with binding of coronavirus S-protein to host cells via the angiotensin-converting enzyme 2 (ACE2) receptors,[9] with subsequent membrane fusion and viral RNA release. As the virus replicates, an expanded innate immune response that is promoted by pathogen-associated molecular patterns (PAMPs) begins to accrue. As with AD immunopathy, this can elicit a complement cascade and lead to the production of inflammatory cytokines and inflammation-associated peptides, including: IL-1, IL-2, IL-4, IL-6, IL-7, IL-10, IL-12, IL-13, IL-17, granulocyte colony stimulating factor (GCSF), macrophage colony-stimulating factor (MCSF), interferon γ-induced protein 10 (IP-10), monocyte chemoattractant protein-1 (MCP-1), MIP-1α, hepatocyte growth factor (HGF), IFN-γ, and TNF-α.[10]

Among the pro-inflammatory cascade induced by this signaling, a key element of COVID-19 is the immunogenic activation of lung antigen presenting cells (dendritic cells and macrophages). These cells can augment the existing inflammatory response; moreover, they are also subject to direct infection by SARS-CoV-2. Once infected, extensive dysregulation occurs, likely involving toll-like receptors (TLR3, TLR7), activation of NF-κB and interferon regulatory factor 3 (IRF3), the production of type

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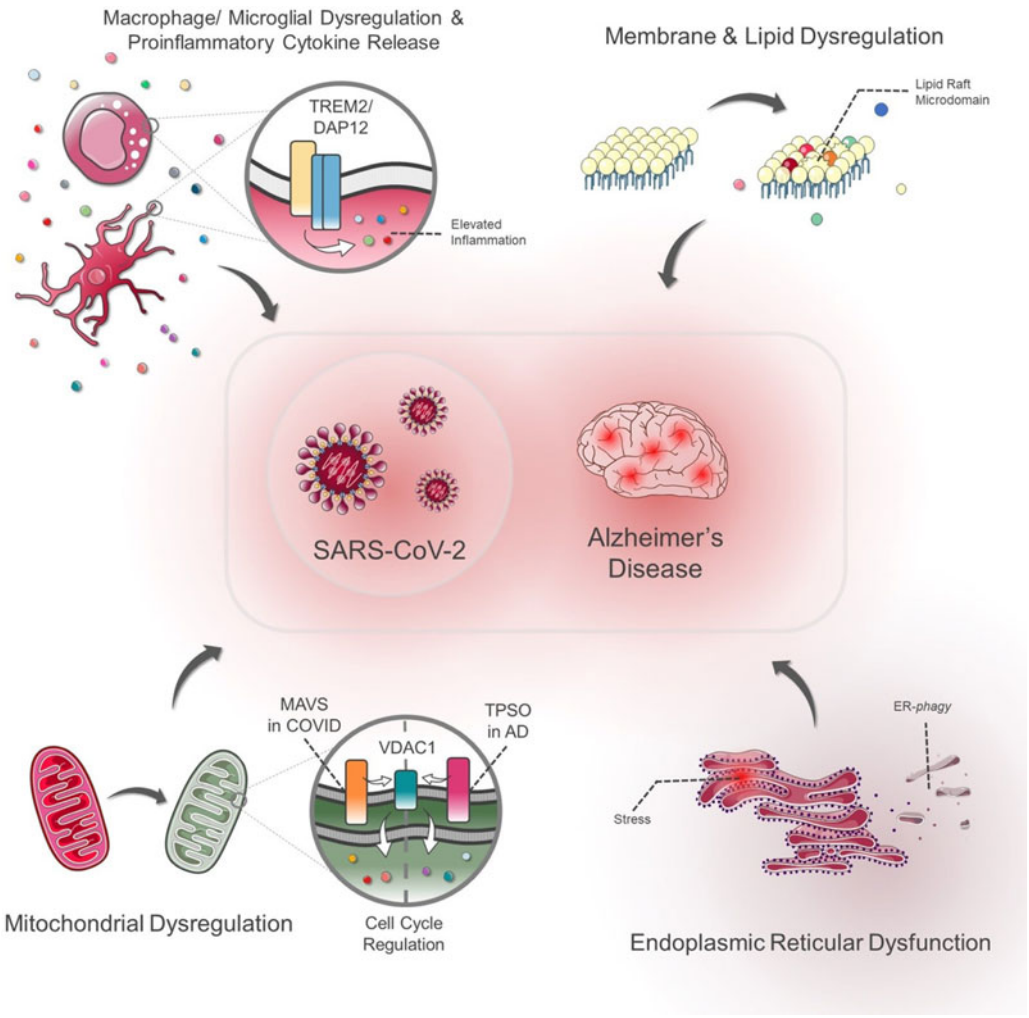

Figure 3: Overlapping therapeutic targets between AD and COVID-19. Similarities in the pathogenesis of Alzheimer's disease and COVID-19 suggest the possibility of repurposing existing AD research and therapeutics against COVID-19. These include elevated inflammation via macrophage/microglial dysregulation – possibly mediated via TREM2/ DAP12 pathways; membrane and lipid dysregulation; mitochondrial dysregulation – mediated via the TPSO pathway in AD, and the MAVS pathway in COVID-19, converging on the VDAC1 channel; and endoplasmic reticular dysfunction – targeting stress or *ER-phagy*.

I interferons (IFN-α /β), and additional pro-inflammatory cytokines.[11] A humoral response is also initiated via mTOR signaling providing cross-protective immunity to virus particles.[12,13]

The pathology of COVID-19 is thus a dual viral and immunopathic assault. Multiple additional elements, such as membrane/receptor regulation, and mitochondrial/endoplasmic reticular integrity contribute to COVID-19 pathology and inevitably complicate the pathogenesis. However, from the simplified dual-hit model, we derive two broad therapeutic avenues: an antiviral approach and an immuno-regulatory approach. The latter shall be the subject of this review due to its overlap with AD.

Targeting Shared AD/COVID-19 Molecular Pathogeneses

AD and COVID-19's shared immunogenic pathologies yield multiple molecular targets at the extracellular (macrophage/microglial, cytokine) and cellular (membrane, cytoplasmic organelle) levels; particularly, the immune-mediated destruction of their respective organ parenchyma yields substantial mechanistic overlap. We conjecture that it is these congruent disease mechanisms which may offer mutual druggable targets (see Figure 3).

Targeting Macrophages/Microglia and Cytokine Release

Macrophages (microglia) and cytokines play key roles in disease progression in both AD and COVID-19. In AD, many years of slow, indolent pro-inflammatory cytokine secretion contribute to chronic neuronal damage; in COVID-19, a rapid release of pro-inflammatory cytokines culminates in an acute lung-damaging hypercytokinemia ("cytokine storm"), a self-targeting injurious inflammatory response syndrome.[14]

In AD, the contributions of immuno-inflammatory processes to disease progression are being increasingly understood. Reactive gliosis, microglial dysfunction, and neuroinflammation, collectively termed "microgliopathy," are now accepted pathological hallmarks of AD. Microgliopathy-associated molecules include two important contributors: the triggering receptor protein expressed on myeloid cells-2 (TREM2), and the 12 kDa DNAX activating protein (DAP12).[15] Upon stimulation, TREM2 engages DAP12, causing the two tyrosines on its immunoreceptor tyrosine-based activation motif to become phosphorylated, activating a signaling cascade promoting cellular functions such as phagocytosis, pro-inflammatory cytokine production, and cytoskeletal rearrangement.

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Microglial regulation has received considerable attention among AD therapeutics due to putative associations with Aβ and tau.[16] Notably, DAP12 also plays a significant general role in coronavirus systemic viral infections.[17] It has been shown to have activating effects on myeloid, natural killer (NK), and T helper cell function during immune responses to an infectious pneumonia.[18,19] Consequently, DAP12 may be a potential AD/COVID-19 overlapping target.

In addition to macrophages/microglia, the pro-inflammatory cytokines are themselves extracellular targets. IL-6 and TNF-α are two pro-inflammatory cytokines significantly implicated in AD and COVID-19. In AD, cytokines, such as IL-6, IL-18, IL-10, TNF-α, and TGF-β1, can affect the metabolism of amyloid precursor protein (APP), augmenting APP expression and impacting Aβ production/deposition.[20] IL-6 has pleiotropic effects inducing APP expression and ultimately extensive chronic gliosis.[21] TNF-α, also actively produced by microglia during inflammation, stimulates BACE1 (Beta-Secretase 1) expression, induces APP mRNA expression in a dose-dependent manner via NF-κB activation, and enhances amyloidogenic processing from APP expressing astrocytes and cortical neurons. In COVID-19, IL-6 and TNF-α are two of the principal cytokines participating in the pulmonary hyper-inflammatory macrophage activation cytokine release syndrome. In accordance with these observations, therapeutics targeting TNF-α have been evaluated in animal models and small human trials suggesting some efficacy against AD;[22] biologics targeting IL-6 (tocilizumab, sarilumab) were evaluated in open label trials suggesting efficacy against COVID-19.

AD and COVID-19 both involve extensive pro-inflammatory contributions to their pathogenesis. DAP12 and cytokines such as IL-6 and TNF-α represent key opportunities for exploiting AD/COVID-19 target overlap when selecting therapeutics for repurposing.

Targeting Membrane Lipids

Membrane structural components, such as lipid rafts and cholesterol, are involved in endocytosis and modulate the processes whereby misfolded neurotoxic peptides such as Aβ and toxic viruses attach and penetrate cells. Accordingly, lipid metabolism is a target-rich opportunity when seeking to exploit AD/COVID-19 pathogenic overlaps.

In AD, lipids play essential roles in disease pathogenesis, particularly through lipid raft macromolecular aggregates.[23] Lipid rafts are membrane microdomains, enriched in cholesterol and sphingolipids (ceramide, sphingomyelin, and glycosphingolipids). They function as cell-signaling mediators and participate in the pathology of AD by promoting the generation, aggregation, and insertion of amyloid into neuronal membranes, as well as enabling the toxic signaling mechanisms that underlie synaptic dysfunction. Beyond altered raft structure, dysregulated lipid homeostasis contributes to AD pathogenesis via various mechanisms involving alterations in intestinal microbiota, the gut–brain axis, neuronal signaling pathways, blood–brain barrier integrity, mitochondrial function, and pro/anti-inflammation balances.[24] Although multiple different lipids individually contribute, cholesterol is especially relevant. Excess brain cholesterol is linked to increased formation and deposition of β-amyloid from APP, through BACE1 and γ-secretase activities. Moreover, elevated cholesterol levels in mid-life are an AD risk factor; cholesterol-lowering statins may reduce this risk.[25,26] Thus, accumulating animal and human studies evidences a mechanistic link between lipid/cholesterol metabolism and AD disease progression.

In COVID-19, multiple veterinary and human studies are likewise indicating a relationship between lipid/cholesterol metabolism and coronavirus infections. This is not surprising given the importance of membrane lipid composition to the processes of viral attachment, penetration, repackaging, and release. Membrane-based cholesterol and in particular species localized to lipid rafts are indispensable biomolecules for coronavirus infection; modulation of levels of host cholesterol facilitates viral entry, replicative complex formation, assembly, egress, and control of the interferon type I response.[27] Clinically, a 12-year follow-up survey of 25 patients who recovered from SARS-CoV infection found that 68% had hyperlipidemia.[28] Among COVID-19 populations, lipidemia and LDL levels also exhibit strong correlations to disease severity and prognosis, though the precise directionality of the trend remains controversial.[29,30]

As dysregulated lipid metabolism and elevated cholesterol are risk factors for both AD and COVID-19, this may be yet another druggable area of AD/COVID-19 overlap.[25,26] This suggests that HMG-CoA (3-hydroxy-3-methyl-glutaryl-CoA reductase) reductase enzyme competitive inhibitors, such as rosuvastatin and related compounds, should be considered in both AD and COVID-19. Moreover, extending beyond conventional agents for cholesterol control, new shared targets for other lipids likewise merit consideration.

Targeting Cytoplasmic Organelles

Among the many organelles contained within the cytoplasm, mitochondria, endoplasmic reticula, and the mitochondrial–endoplasmic physical interface provide target-rich opportunities at the AD/COVID-19 pathogenesis overlap.

Mitochondria

Mitochondria from AD patients differ from those of non-AD individuals morphologically, functionally, and in terms of gene expression.[31] Extensive data suggest that mitochondria instigate and/or mediate diverse AD pathologies. Debate continues over the origin of these AD mitochondrial changes.[32] Some data suggest mitochondrial dysfunction temporally occurs upstream from proteopathies, indicating a primary mitochondrial pathology may supersede amyloid and tau pathologies; other data suggest that mitochondrial dysfunction is a consequence of amyloid proteopathy but nonetheless contributes to ongoing neural damage once triggered. In terms of specific molecular targets, recent work has implicated translocator protein (TSPO), an outer membrane mitochondrial protein that locates cytosol cholesterol to mitochondrial membranes.[33] TPSO is present in the glial cells that respond to neuroinflammation and regulate the opening of the mitochondrial permeability transition pores controlling entry of molecules necessary for mitochondrial function. TSPO is a pro-apoptotic protein which functions via its interaction with the voltage-dependent anion channel 1 (VDAC1) protein, the most abundant outer membrane mitochondrial protein; VDAC1 is the organelle's gatekeeper for the passage of ions, nucleotides, and metabolites, playing a central role in apoptosis regulation through its interaction with apoptotic and anti-apoptotic proteins of the Bcl-2 (B-cell CLL/lymphoma 2) protein family.[34] Notable, TSPO is upregulated in the brain of AD patients and is generally thought to be conclusively linked to AD.

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In viral infections such as COVID-19, mitochondria are well recognized as pivotal organelles in controlling signaling pathways essential to the host response in restraining viral infections.[35] Specifically, a major role in antiviral defense is played by mitochondrial antiviral signaling (MAVS) protein, an adaptor protein that coordinates the activation of interferon-inducing pathways and autophagy at the mitochondrial level by involving activation of NF-κB and (IRF3 leading to the production of type I interferons (IFN-α /β) and additional pro-inflammatory cytokines.[36,37] Co-localized with Bcl-2 proteins and essential for antiviral innate immunity, MAVS is a 540 amino acid outer membrane mitochondrial protein that consists of three components, an N-terminal caspase activation recruitment domain, a proline-rich domain, and a transmembrane C terminal domain, which induce apoptosis in virally infected host cells by interacting with the caspase 8 protease.[38] Recently, it was demonstrated that mitochondrial-located MAVS protein mediates its pro-apoptotic activity by associating with VDAC1 and modulates VDAC1 protein stability via the ubiquitin-proteasome pathway.

The significance of mitochondrial changes in AD and COVID-19 is an evolving area of interest, and mitochondrial dysfunction represents a reasonable therapeutic target in the realm of AD/COVID-19 overlap, with particular focus on outer mitochondrial membrane proteins such as VDAC1.

Endoplasmic Reticulum

The ER is increasingly recognized as a molecular contributor to the pathogenesis of AD.[39] ER stress has been observed in postmortem AD brains, and ER stress is known to arise with the accumulation of misfolded or unfolded proteins, such as Aβ and tau. These mechanisms may be mediated by inositol-requiring enzyme 1 (IRE1), protein kinase R-like endoplasmic reticulum kinase (PERK), and activating transcription factor 6 (ATF6) stress sensors.[40] In addition to these stress responses, cross-talk between the ER and adjacent mitochondria may also be impacted in AD. Sub-compartments of ER are in physical and biochemical contact with mitochondria via raft-like lipid regions referred to as mitochondria-associated membranes (MAMs), which play important roles in lipid synthesis, calcium homeostasis, and apoptotic signaling.[41] Within the ER-mitochondria, MAMs bridging complex, inositol-1,4,5-triphosphate receptors facilitate biochemical cross-talk. Upregulated MAM-associated proteins are found in AD brains as well as (APP) Swe/Lon mouse models and can be detected before the appearance of plaques.[42]

In COVID-19, vesicle trafficking within the ER of host cells is important in coronavirus replication;[43] the replicase-transcriptase machinery and other viral structural proteins assemble within the host ER, making it an essential cellular component for viral genome replication and capsid assembly in the formation of new virus particles, which germinate in the ER-Golgi intermediate compartment prior to fusion with the plasma membrane and viral release.[44,45] This process induces ER stress analogous to that occurring in association with AD pathology, involving both MAVS and MAM proteins, and mimicking many pathognomonic elements of an unfolded protein response.[46]

In both AD and COVID-19, ER function and stress are intimately linked to autophagy, a catabolic process involving the engulfment of cellular material by a double-membrane structure, the phagophore, which subsequently closes into an autophagosome vesicle sequestering cargo and debris which is degraded following fusion with a lysosome. Autophagy is a bulk process that unselectively degrades cellular material as required for cellular upkeep. However, autophagy can also selectively target distinct organelles requiring turnover. The specific elimination of the ER via a selective form of autophagy is now recognized as a unique biochemical process termed ER-phagy.[47] ER-phagy is specifically involved in both AD and COVID-19 and constitutes another potentially druggable area of biochemical overlap between these two disorders.

Repurposing Drugs

Over the course of the past 25 years, there have been over 200 clinical trials assessing agents as either symptomatic or disease modifying for the treatment of AD. Although almost all have failed to show efficacy against AD's symptomatology, they provide a number of chemical entities which have been well studied and deemed safe for human exposure. As representative examples, we discuss curcumin, pioglitazone, *scyllo*-inositol (SI), tramiprosate, furosemide, ibuprofen, and sildenafil as potential agents against COVID-19.

Therapeutic Agents Repositioned for AD

Curcumin

Derived from the rhizomatous, ginger-like plant *Curcuma longa*, curcumin is a natural polyphenol with well-evidenced anti-inflammatory and anti-microbial activities. Its anti-inflammatory properties are thought to derive from a series of synergistic mechanisms, ranging from free-radical scavenging, the modulation of antioxidant enzymes as well as the inhibition of free-radical generating systems including cyclooxygenases.[48,49] It may also downregulate activation of NF-κB signaling cascades and thus mediate a broader, systemic anti-inflammatory effect.[50,51] In AD models, curcumin was also shown to be a potent inhibitor and destabilizer of neurotoxic amyloid species, even reducing the senile plaque burden in APPswe/PS1dE9 mouse models.[52,53] It may also be effective in the chelation of metal species and reducing cholesterol esters – both potent risk factors in the aggravation of AD protein and immune pathologies.[53]

These emerging associations, aided by a relative ease of access and the less stringent regulations surrounding natural supplements, have driven a sensationalized, and largely unevidenced, belief of a potential therapeutic benefit in AD. Yet, no trial has demonstrated any significant effect on either disease onset or prognosis with curcumin or its derivatives. This may be partly attributable to the poor bioavailability of the bulky curcumin molecule in the aqueous extracellular environment. These same characteristics also compromise its ability to cross the blood–brain barrier and thus limit its efficacy as a neurological agent.

In the treatment of COVID-19, however, formulations of curcumin have shown some promise. When packaged in nanomicelles, Saber-Moghaddam *et al.* report 160 mg of curcuminoids daily was able to resolve COVID symptoms, including fever, chills, tachypnea, and myalgia significantly more expediently, and that hospitalization, supplemental oxygenation parameters as well as overall disease resolution were meaningfully improved.[54] Multiple trials on various forms of curcumin remain ongoing. Though curcumin has yet to effective in the treatment of AD, the extensive data on its anti-inflammatory roles and its optimal formulation, both for efficacy and bioavailability, may be of relevance in the trials of COVID-19.

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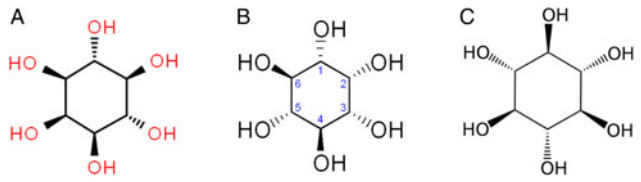

Figure 4: Molecular structures of inositol isomers. Inositol (A) is a collection of nine different stereoisomers of a hexa-substituted cyclohexane polyol. The most common isomer is *myo*-inositol (B), which is cis-1,2,3,5-trans-4,6-cyclohexanehexol. *Scyllo*-inositol (C) has undergone trials as an amyloid anti-aggregant in AD.

Pioglitazone

Pioglitazone is a thiazolidinedione, originally developed as an anti-hyperglycemic adjunct in the 1980s and 90s.[55] It targets peroxisome proliferator-activated receptors to reduce the effects of insulin resistance in tissues. In the brain, modulating these insulin signaling pathways was associated with a reduction of multiple inflammatory, cell death, and proliferation associated pathways, including IR, IRS-1, AKB, p-CREB, and Bcl-2.[56–58] Crucially, in animal models, pioglitazone also mediated amyloid plaque clearance, reduced tau hyperphosphorylation, and aided synaptic plasticity.[59–61] These outcomes, along with robust safety and pharmacologic profiles, motivated a pair of large phase III trials; both, however, were terminated for lack of efficacy. It remains unclear why the trails failed, though in accord with the complexity and chronicity of all dementia trials, it is conceivable that multiple study and clinical parameters, especially the many years of indolent disease progression preceding the development of symptoms, have been contributory to trial failures.

In spite of these failures, pioglitazone is a well-established inflammatory mediator. Xie *et al.* demonstrated that even amongst individuals without hyperglycemia, pioglitazone significantly reduced IL-6 and TNF-α.[62] With extended use, astrocyte, lymphocyte, and other inflammatory cytokine production modalities were attenuated.[61] Especially relevant in the management of SARS-CoV-2, pioglitazone may also act on pulmonary inflammation and fibrosis, with multiple studies observing diminished inflammatory markers in animal lung and lavage samples.[63]

A major barrier in the treatment of COVID-19 is the management of acute symptomology. Typically, low even subclinical dosing of pioglitazone was administered for weeks to observe a gradual clinical effect. As it was intended for the treatment of chronic and progressive diseases, this is expected. However, the acute management of COVID-19 will inevitably require breakthrough dosing and emergent management. The secondary outcome profile will also be critical; if high-dose administration leads to uncontrolled hypoglycemia or hypersensitivity to insulin, these may complicate the management of infection.

Inositol

Inositol is a carbocyclic sugar that mediates cell signal transduction in response to a variety of chemical messengers, hormones, and growth factors. Structurally, inositol is a hexa-substituted alcohol of cyclohexane; epimerization of the six hydroxyl groups generates nine stereoisomers (see Figure 4). *Myo*-inositol (MI) is the most prominent stereoisomer and plays a central role as the structural platform for a number of inositol phosphate secondary messengers. It also serves as an important structural component of membrane phospholipids, such as phosphatidylinositol.

In AD, a ^{1}H magnetic resonance spectroscopy study demonstrated elevated brain MI levels in the pre-dementia in adults with Down's syndrome, suggesting a role for MI as an AD diagnostic.[64] SI, another stereoisomer that is relatively rare in nature, has also been considered as a therapeutic for AD. SI has been reported to stabilize the nontoxic oligomers of Aβ and to inhibit their toxic aggregation, by coating the surface of Aβ protofibrils and disrupting their stacking into fibrillar aggregates; an analog series of SI derivatives was synthesized and evaluated revealing that all six inositol hydroxyl groups were involved in fibrillar aggregation inhibition.[65] In the late 1990s, McLaurin and coworkers pursued a clinical trial of SI in AD which failed to show improvement.[66]

In COVID-19, Bizzarri *et al.* have postulated that MI could be used to ameliorate the toxic pulmonary inflammatory response.[67] This suggestion is based on the observation that MI has been successfully used to treat newborn respiratory distress syndrome, achieving this goal by downregulating the inflammatory response via reduction of IL-6 levels known to mediate the inflammatory cascade. Since MI is essentially devoid of major side effects, they have speculated regarding its utility in the treatment of critically ill COVID-19 patients.

Glycosaminoglycan Mimics

Glycosaminoglycans (GAGs) are long linear mucopolysaccharides consisting of repeating disaccharide units; the repeating unit typically consists of an amino sugar, along with a uronic sugar or galactose. GAGs are essential molecules, covalently connecting to proteins to form proteoglycans. GAGs are highly negatively charged polymers that can also sequester physiologically important proteins and strongly bind water and ions. Heparan sulfate is a prototypic GAG with a polyanionic structure arising from multiple geometrically positioned sulfate groups.

In AD, GAGs (specifically with sulfate moieties) are important molecular co-conspirators facilitating protein misfolding and oligomerization. They facilitate interactions between monomeric or oligomeric Aβ and neuronal/glial cell surfaces possibly involving the serpin-enzyme complex receptor, the alpha7nicotinic acetylcholine receptor (alpha7nAChR), the receptor for advanced glycosylation end-products, and formyl peptide receptor-like 1.[68] Our group further observed that at an atomistic level, Aβ may interact directly with GAGs via its HHQK domain to mediate portion of neuronal membranes.[69]

Since heparin is an already available GAG mimetic, various groups have demonstrated its capacity to bind to Aβ and prevent subsequent oligomerization. However, heparin is a potent anticoagulant and inappropriate for chronic use in AD's elderly cohorts. Accordingly, in the 1990s, we synthesized numerous polysulfonated small molecule GAG mimetics, ultimately pursuing clinical trials with tramiprosate (3-amino-1-propanesulfonic acid) for AD and eprodisate (1,3-propanedisulfonic) for renal failure in systemic amyloidosis – both failed to show efficacy in Phase III human trials (see Figure 5).[70]

For COVID-19, Mycroft-West *et al.* have suggested repurposing heparin as a GAG mimetic for uses as a coronavirus antiviral.[71] They put forth this suggestion after using surface plasmon resonance and circular dichroism to measure the interaction between the SARS-CoV-2 Spike S1 protein receptor-binding domain (SARS-CoV-2 S1 RBD) and heparin.[72] Coronavirus contains four structural proteins, including spike (S), envelope (E), membrane (M), and nucleocapsid (N) proteins, with the S protein mediating viral entry into host cells by binding to the host receptor through the RBD in the S1 subunit and then fuzing the viral and host membranes through the S2 subunit.[73] SARS-CoV recognizes the ACE2 enzyme as its receptor. However, full pathological expression of

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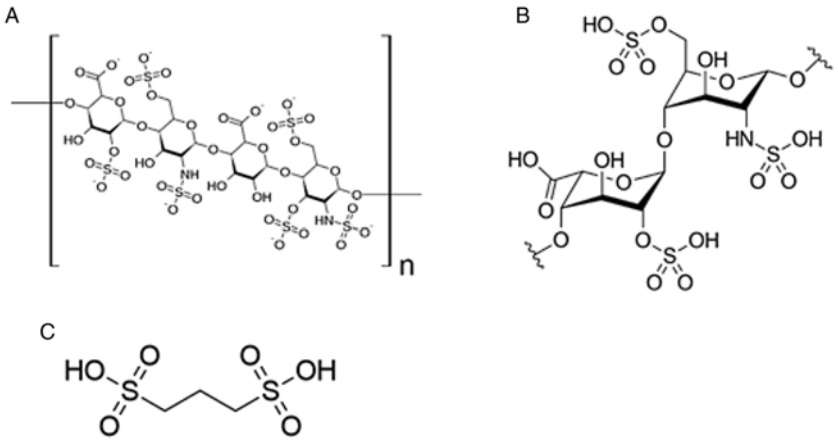

Figure 5: Molecular structures of heparan sulfate, heparin sulfate, eprodisate. Heparan sulfate (A) (HS) is a linear polysaccharide that occurs as a proteoglycan (HSPG) in which two or three HS chains are attached in close proximity to cell surface or extracellular matrix proteins. Heparin (B) is a smaller glycosaminoglycan polysaccharide polymer, structurally related to heparan, and consists of a variably sulfated repeating disaccharide unit; the most common disaccharide unit is composed of a 2-O-sulfated iduronic acid and 6-O-sulfated, N-sulfated glucosamine, IdoA(2S)-GlcNS(6S). Eprodisate (C) (1,3-propanedisulfonate) is a negatively charged, sulfonated small molecule that has structural similarities to heparin and heparan sulfate; it is a glycosaminoglycan mimetic with sulfate group positioned geometrically to mimic those in heparin and heparan.

coronavirus attachment and entry requires not only ACE2 but also viral binding to host cell heparan sulfate GAG adjacent to and part of the expanded ACE2 receptor complex. Mycroft-West *et al.* exploited structural similarities between heparan sulfate and heparin, using heparin as a small molecule GAG mimetic to bind to the virus, thereby blocking its capacity to bind to host cells. Based upon this molecular interaction they postulated the rapid implementation of a first-line therapeutic by repurposing heparin whilst tailor-made, GAG-mimetic antivirals are being developed. Heparin is a well-known agent, but its use is complicated by its significant anti-coagulant activity, especially in individuals critically ill with COVID-19. Accordingly, there may be a place for failed GAG-mimetic agents, such as eprodisate, as safer substitutes for heparin.

Furosemide

Furosemide is a Food and Drug Administration approved loop diuretic used in the treatment of hypertension and associated edema in cardiac, renal, and hepatic failures.[74] Through inhibition of the Na(+)-K(+)-2Cl(-) cotransporter (NKCC2),[75] furosemide works by blocking sodium and chloride tubular reabsorption in the proximal and distal tubules, and the thick ascending loop of Henle, resulting in decreased extracellular accumulation of fluid in cardiac and renal pathologies.[76]

Previous reports have indicated that antihypertensive use is associated with a reduced risk of AD and similar dementing disorders.[77] In *in vivo* models of AD, furosemide was found to enhance kidney-mediated clearance of Aβ, rescue cognitive impairments, and attenuate astrogliosis and neurodegeneration.[78] Moreover, *in vitro* studies using Tg2576 mice identified furosemide to reduce oligomerization of Aβ40 and Aβ42 and dissociate aggregated oligomers of Aβ42 to prevent AD pathologies.[79] Wang *et al.* further observed the potential of furosemide as a probe molecule in alleviating neuroinflammation in AD.[80] Furosemide induced the anti-inflammatory microglial M2 phenotype through reduced production of pro-inflammatory markers such as TNF-α, IL-6, NO, COX-2, and inducible nitric oxide synthase (iNOS), promotion of phagocytosis, and elevated secretion of anti-inflammatory IL-1RA and arginase. They then synthesized and optimized furosemide analogs to inhibit Aβ aggregation and neuroinflammation, demonstrating the therapeutic potential of furosemide-like drugs in AD.[80]

Following COVID-19-induced hypercytokinemia, excessive production of pro-inflammatory cytokines, including IL-6 and TNF-α, underlies the resulting multi-organ pathologies. Furosemide treatment on peripheral blood mononuclear cells (PBMCs) derived from normal subjects was shown to reduce production levels of pro-inflammatory cytokines IL-6, IL-8, and TNF-α.[81] Moreover, increasing doses of furosemide were found to reduce secretion of IL-6 and TNF-α by placentas and PBMCs in normal pregnancy.[82] It has also been reported that furosemide drives macrophages towards an anti-inflammatory cytokine profile, hinting at its immunomodulatory effects.[83] The beneficial clinical effects of furosemide are further supported by multiple clinical trials which have identified alleviated production of pro-inflammatory cytokines in patients with pulmonary pathologies including chronic lung disease, bronchopulmonary dysplasia, and tachypnea.[84–88]

Considering that pulmonary edema is thought to be due to the cytokine storm, a retrospective observational study was conducted on patients with COVID-19; tomographic evidence of pulmonary edema and volume overload justified a standard treatment using furosemide and a Negative Fluid Balance (NEGBAL) approach.[89] Promising clinical responses to NEGBAL have been reported.[90] Moreover, Kevorkian *et al.* have suggested repurposing furosemide in combination with early short-course corticosteroids for use in non-critically ill COVID-19 patients to reduce the risk of mechanical ventilation and/or mortality.[91] In addition, an ongoing Phase 2/3 clinical trial is assessing the efficacy of nebulized furosemide for treatment of pulmonary inflammation and respiratory failure in intubated and mechanically ventilated COVID-19 patients.[92]

The need for a widely available therapeutic to address the urgent need for ameliorating COVID-19 hypercytokinemia is growing rapidly. While current biological therapeutics such as siltuximab (an IL-6 antagonist) may target similar inflammatory pathways as furosemide, they have a relatively high immunogenic potential.[93] Therefore, as serum levels of IL-6 and TNF-α are dominant predictors of COVID-19 severity and death[94] and the fact that furosemide has been reported to be an inhibitor of both,

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repurposing this approved drug renders an optimistic therapeutic approach.

Non-Steroidal Anti-Inflammatory Drugs

Non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen are used in the treatment of mild-to-moderate pain and inflammation.[95] Mostly via nonselective and reversible inhibition of the cyclooxygenase enzymes COX-1 and COX-2, NSAIDs exert their analgesic and anti-inflammatory properties. A study by Zhang et al. found that ibuprofen treatment in a mouse model of AD led to suppression of inflammatory factors normally upregulated in AD including TNF-α, IL-1β, and NF-κB. They also found that through suppression of inflammation, the function of P-glycoprotein (P-gp) causing Aβ efflux was also increased, suggesting that ibuprofen may reduce AD pathology through a P-gp-mediated mechanism.[96] Interestingly, in an aged mouse model of AD, ibuprofen treatment led to a reduction in the levels of oxidative damage and ultimately reduced microglial activation and plaque deposition.[97] Moreover, the beneficial effects of ibuprofen on cognition have also been demonstrated using a transgenic mouse model of AD in which treated mice achieved similar scores as control normal mice on complex visual-spatial learning tasks.[98] A bioinformatic analysis also revealed that ibuprofen treatment was associated with altered expression of genes associated with AD, suggesting that it may be a beneficial long-term therapeutic.[99]

While during early stages of the pandemic there were concerns of exacerbated COVID-19 through use of NSAIDs, recent evidence suggests otherwise. As COVID-19 pathogenesis is largely driven by mediators of inflammation, repurposing NSAIDs which have anti-inflammatory effects is a potential therapeutic approach. A number of studies have suggested that early administration of NSAIDs may reduce the COVID-19 hyper-inflammatory response.[100,101] Moreover, as NSAIDs have been shown to reduce numerous pro-inflammatory cytokines involved in the initiation of cytokine storm,[102] their use in COVID-19 may be of benefit. Other mechanisms by which NSAIDs may be beneficial include its effects on dampening of the NF-κB pathway,[103] inhibition of caspases,[104] reducing prostaglandin-mediated edema,[105] and via modulatory effects on iNOS inflammatory cascades.[106] Repurposing NSAIDs for therapeutic use in both AD and COVID may therefore be a rational approach.

Sildenafil

Sildenafil is a selective cGMP-specific phosphodiesterase-5 inhibitor used primarily for the treatment of erectile dysfunction and pulmonary arterial hypertension.[107] Considering that SARS-CoV-2 disrupts pulmonary perfusion regulation, oral administration of sildenafil to reduce pulmonary vascular resistance and inflammation may be a rational therapeutic approach in mild to severe cases.[108–110] A recent study observed that sildenafil treatment for COVID-19-induced acute respiratory distress syndrome was well tolerated and led to enhanced cardiac biomarkers as well as echocardiographic outcomes.[111] Thus, sildenafil may be a potential therapeutic in pulmonary complications of COVID-19 due to its easier use compared to nebulized vasodilator therapies such as inhaled NO which are unstable and difficult to administer.[108]

As sildenafil affects vascular function through its activation of the NO signaling cascade,[112] it may be a promising pharmaceutical intervention in AD. A single use of sildenafil in AD patients was demonstrated to improve cerebral oxygen metabolism and function.[113] Using an endophenotype disease methodology for AD drug repurposing, it was identified that sildenafil use was associated with a 69% decreased risk of AD, even in patients with coronary artery disease, hypertension, and type 2 diabetes. Sildenafil was also shown to reduce expression of phospho-tau in neuron models derived from AD patients.[114] In a mouse model of AD, sildenafil was shown to reduce hippocampal levels of Aβ, reverse memory, and cognitive deficits and induce an anti-inflammatory response to prevent neuroinflammation.[115] A separate study also reported similar findings using an AD mouse model in which sildenafil reverse cognitive deficits reduced hippocampal tau hyperphosphorylation and increased the expression of brain-derived neurotrophic factor.[116] Additionally, in rats it was identified that sildenafil reduced levels of vascular cell adhesion molecule-1 (VCAM-1), TNF-α, and oxidative stress, while increasing levels of vascular endothelial growth factor, thereby hinting at its potential modulatory effects.[117] Thus, there is strong evidence for the dual beneficial effects of sildenafil on AD pathology and COVID-19 and may be a rational drug repurposing strategy.

Conclusions

AD and COVID-19 are both pandemics in their own right. Over 6.5 million North Americans presently have AD, and this will increase by more than 500,000 by 2025.[118] Following current trends, the prevalence is projected to reach 13.8 million by 2060.[118] COVID-19 on the other hand may be lethal within 2 weeks of its first symptoms, with approximately 500,000 new cases and 30,000 deaths per month worldwide over the first 3 months of 2020. By November 2022, there have been more than 630 million cases of COVID-19 worldwide with over 6.5 million deaths. Arising from its rapid infectivity, lethality, unpredictability, and changeability, the need for effective therapies for COVID-19 is an ongoing pharmacological urgency for which the standard protracted drug development timelines accepted in AD research are not feasible. Although fundamentally different diseases, AD and COVID-19 share a wide range of pathogenic commonalities at the membrane, cytoplasmic, and extraneuronal (microglial, cytokine) levels. These may extend to the druggability of these targets enabling cross-over applicability of the corresponding drugs to both diseases. Arising from the AD/COVID-19 overlap, in the short term, agents developed for the Alzheimer's pandemic might be repurposed for the COVID-19 pandemic; conversely in future years, agents developed for the COVID-19 pandemic may be viable platforms for the Alzheimer's pandemic.

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