

Review

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[Coad Thomas Dow](#)* and Laith Kiddess

Posted Date: 10 February 2023

doi: 10.20944/preprints202302.0173.v1

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Review

Proposing Intranasal Rifampin for Alzheimer's Disease and the Other Age-Related Neurodegenerative Proteinopathies

Coad Thomas Dow ^{1,2,*} and Laith Kidess ³

¹ Department of Ophthalmology and Visual Sciences, McPherson Eye Research Institute, Madison, WI 53705, USA

² Mindful Diagnostics and Therapeutics, Eau Claire, WI 54701, USA

³ Department of Biochemistry, University of St. Thomas, St. Paul, MN 55105, USA

* Correspondence: ctomdow@gmail.com or ctdow@wisc.edu; Tel.: +1-715-577-5656; 4421 Old School Court, Eau Claire WI 54701, USA

Abstract: This article proposes the use of intranasal rifampin as a means to improve protein homeostasis and disaggregate misfolded proteins in the age-related neurodegenerative proteinopathies. Alzheimer's disease, Parkinson's disease, multi-system atrophy, Lewy body dementia, frontotemporal dementia, amyotrophic lateral sclerosis and Huntington's disease are all, at the core, proteinopathies. Although these diseases vary greatly in the specific disease-associated proteins, anatomic sites of the abnormal protein deposition and clinical presentations, what they have in common is disruption of normal "housekeeping" functions related to protein homeostasis, proteostasis. The prospect of pharmacologically augmenting autophagic capacity with a known drug repurposed to improve proteostasis is attractive; to accomplish these ends with an inexpensive drug with relative ease of delivery adds to the attractiveness. Rifampin can be delivered to the brain via the intranasal route. Rifampin has been used for decades primarily against mycobacterial infection; it has been given with intravenous, oral, intrathecal and topical routes including as eyedrops and nasal spray. Rifampin disaggregates toxic oligomers *in vitro*; given intranasally, rifampin improves memory and clears pathologic proteins in animal models of the proteinopathies. Rifampin acts as both a gatekeeper and a housekeeper against the abnormal proteins of these diseases. This article suggests the merit of a clinical trial with intranasal rifampin to boost protein homeostasis in the most common age-related neurodegenerative proteinopathy, Alzheimer's disease. The primary outcome of such a trial is change in risk of Alzheimer's pathology as measured by plasma-based amyloid peptide 42/40 testing pretreatment and follow-up testing after 6 months of intranasal rifampin.

Keywords: rifampin; proteinopathies; permeability glycoprotein; intranasal; bi-directional; Alzheimer's; Parkinson's; Lewy body dementia; multiple system atrophy; huntington's; amyotrophic lateral sclerosis/frontotemporal dementia spectrum

The age-related neurodegenerative diseases include Alzheimer's disease (AD), Parkinson's disease (PD), Lewy body dementia (LBD), Multiple System Atrophy (MSA), Huntington disease (HD) and amyotrophic lateral sclerosis/frontotemporal dementia spectrum (ALS-FTD). While these are all distinct clinical and pathologic entities, they share a cardinal feature: loss of the disease-related proteins' normal physiologic function with a change into accumulated, misfolded and neurotoxic proteins [1,2].

Putatively, the associated proteins are amyloid- β and tau for AD, synuclein for PD, LBD and MSA, huntingtin for HD and transactive DNA-binding protein 43 (TDP-43) for ALS-FTD [3]. Collectively these diseases are age-related neurodegenerative proteinopathies, or protein misfolding

neurodegenerative diseases. The result is disease-specific pathologic protein aggregation in the central nervous system with neuronal loss in disease-specific anatomical locations [4].

Protein homeostasis or "proteostasis" represents the regulatory process resulting in normal intracellular equilibrium of functional and "healthy" proteins; this includes protein synthesis, folding and degradation. Essential for cell viability and function, the proteostasis "housekeeping" function removes damaged, misfolded, and aggregated proteins via the ubiquitin-proteasome system and the autophagy-lysosome pathway [2]. While the removal of toxic misfolded proteins is critical for all cells, it is particularly important in post-mitotic neurons [5]. Post-mitotic neurons cannot utilize mitosis as a means to dilute toxic proteins which makes them uniquely vulnerable to impaired toxic protein removal [6], this vulnerability is aggravated with advancing age [7,8].

A mainstay of proteostasis is autophagy, the phylogenetically conserved housekeeping function critical for removal of toxic proteins in all cell types, including neurons. Moreover, astrocytes and subtypes of microglia play important roles in the phagocytosis and eventual autophagic elimination of neurotoxic proteins [3]. Autophagy ensures a basic supply of recycled amino acids, sugars, lipids and other products of autophagic catabolism [9].

Any strategy to lessen these proteinopathies by boosting autophagy would be a welcome addition to offset the largely ineffective interventions currently available [10,11]. Rifampin (PubChem CID: 6918244) is a well-known antibiotic primarily used to treat mycobacterial diseases such as tuberculosis and leprosy [12]. An observation was made 30 years ago wherein elderly leprosy patients seemed to be protected against Alzheimer's disease; rifampin was the therapeutic agent used to treat their leprosy [13,14]. The remainder of this paper will discuss rifampin and its role in the clearance of neurotoxic proteins associated with age-related neurodegenerative diseases.

Rifampin

In 1957, a newly discovered bacterium - *Nocardia mediterranei*, was isolated by Piero Sensi and Maria Timbal [12]. Metabolites from this bacterium produced new molecules with antibiotic properties; one of which was rifampin. By 1968, it was clear that rifampin had an important role in therapy for mycobacterial infections [12]. Rifampin is delivered orally [15,16], intravenously [16], topically [17], by inhalation for pulmonary mycobacterial infection [18,19], as eye drops [20] and as nose drops [21,22].

Rifampin is readily absorbed from the gastrointestinal tract (90%) Rifampicin reaches maximal serum concentration in 1–4 h after application and its plasma half-time is 2–5 h [23]. Intravenously given, rifampin has the same distribution as the oral route. Eighty-nine percent of rifampin is bound to plasma proteins; this accounts for both the well-known first pass metabolism and toxicity for the liver [24].

Notwithstanding the known hepatic risk, rifampin has been given in much higher doses for rifampin-sensitive tuberculosis [25,26] and particularly for tuberculous meningitis [16]. The rifampin standard-of-care oral dose is 10 mg/kg with increase dosage ranging to 35 mg/kg and intravenous dosing at 20 mg/kg. Treating tuberculous meningitis, the minimal inhibitory concentration (MIC) for rifampin in the cerebral spinal fluid (CSF) is >1 mg/L. Standard-of-care dosing does not achieve this MIC; however, higher oral and intravenous dosing both exceed this therapeutic level [16].

Aside from its central role in treating mycobacterial disease, rifampin is found to impart brain protective properties; this extends to neurodegenerative diseases AD and PD as well as meningitis, stroke and optic nerve injury [27]. In PD, rifampicin inhibits alpha-synuclein fibrillation and disaggregates existing fibrils [28]; in AD, rifampin inhibits amyloid oligomerization [29] and enhances clearance of amyloid in an animal model [30].

Clinical trials targeting amyloid in patients already having reduced cognitive function due to AD show that the therapeutic interventions at that juncture have little effect on disease course [31–33]; this suggests that preventive therapy should start prior to clinical symptoms. Interventional efforts with rifampin failed in cohorts of mild and moderate AD individuals [34]. Conversely, when rifampin was used in preclinical and prodromal AD, it showed preventative effects [35]. This clarifies the need for novel plasma biomarkers identifying AD risk that then can be used in clinical trials of

individuals with prodromal AD [36]. Though attractive as repurposed rifampin may be for AD clinical trials, as mentioned, it is notably hepatotoxic [37] and has multiple adverse drug-drug interactions [38].

What is the evidence that repurposed rifampin could aid in the fight against the age-related neurodegenerative proteinopathies?

Rifampin in *In Vitro* Studies of Age-Related Neurodegenerative Proteinopathies

As cited, rifampin mediates synuclein fibrillation and promotes disaggregation of already formed synuclein fibrils [28] suggesting a therapeutic application for the synucleinopathies of PD, DLB and MSA. In a study of several candidate compounds tested in cell-free conditions, rifampin showed the strongest inhibitory activity against oligomer formation of amyloid, tau and synuclein [29]. Remarkably, the activity of rifampin against aggregated and neurotoxic amyloid has been known for nearly thirty years [39]. Moreover, rifampin inhibits microglial inflammation and promotes neuronal viability [40]; this reduced microglial inflammation was also found with the use of rifampin and its derivative, rifampin quinone against inflammatory responses induced by synuclein aggregates in cell culture [41].

Rifampin (Systemic) in Animal Models of Neurodegenerative Proteinopathies

Rifampin reduces abnormal aggregated synuclein in a transgenic mouse model of MSA which is accompanied by reduced neurodegeneration [42]. Rifampin clears amyloid in an AD mouse model and this enhanced clearance is facilitated by efflux upregulation [30]. Intraperitoneal injection of rifampin ameliorated cognitive impairment of an AD mouse model and protected the hippocampal neurons via enhanced autophagy [43]. Rifampin-loaded nanoparticles improved spatial learning and memory of AD mice paralleling reduced amyloid deposition [44]. A broad defensive role of rifampin in animal models of experimental dementia is reported in a rat-model of aluminum chloride-induced dementia wherein a recuperative response was seen with rifampin that was associated with improved memory, anti-oxidative, anti-inflammatory and amyloid lowering effects [45].

Rifampin (Intranasal) in Animal Models of Neurodegenerative Proteinopathies

Due to the previously noted rifampin-induced liver injury via systemic administration the consideration of intranasal delivery of rifampin is attractive as it avoids hepatic first pass metabolism and offers direct CNS bioavailability [46]. Umeda and associates have shown the advantage of intranasal rifampin over oral delivery in a mouse AD model; the benefit included improved memory and reduction in AD pathology including amyloid oligomer accumulation, abnormal tau phosphorylation and synapse loss [47]. They expanded their work with nasal rifampin to a mouse model of DLB showing improved cognition and reduced synuclein oligomers [48]. In another animal study, intranasal rifampin (combined with resveratrol), lessened amyloid, tau and synuclein pathology and significantly improved cognition

[49]. In yet another study by Umeda, nasal rifampin was found to inhibit tau oligomer propagation in an animal model of AD tauopathy. This study was most interesting in that the tau inoculum was sourced from the brain of a human AD patient [50]. The range of intranasal rifampin benefit across the neurodegenerative proteinopathies is evidenced in a successful animal study using genetic animal models of FTD and ALS, hexanucleotide repeat expansion-related neuropathy [51].

Rifampin (Systemic) in Human Trials of Neurodegenerative Proteinopathies

A Canadian rifampin clinical trial was published in 2004; it included one hundred one participants in two groups: probable AD and mild to moderate AD. This trial showed those taking oral rifampin (along with doxycycline) exhibited less decline in a standardized AD assessment (SADAScog) than placebo [34]. Unfortunately, these data could not be replicated [52]. Addressing the dose and duration of the unsuccessful study, a trial of oral rifampin given at a dose of at least 450 mg/day for at least one year significantly improved both metabolic function and cognitive status

suggesting that the previous unsuccessful trial with rifampin was due to starting too late with too low a dose for too short of an interval [53].

Rifampin (Intranasal) in Human Trials of Neurodegenerative Proteinopathies

The purpose of this article was to make an argument for clinical trials utilizing intranasal delivery of rifampin. Rifampin's significant brain neuroprotection along with the cerebral anti-inflammatory effects should prompt a clinical trial due to the overwhelming untoward demographics presented by the age-related neurodegenerative proteinopathies [54]. Ideally, this repurposed use of rifampin would be employed in those identified to be at high risk for neurodegenerative proteinopathies. For example, participants could include individuals identified as high risk for AD via positive amyloid-PET scan or via the plasma-based PrecivityAD™ [55]. Similarly, participants could be identified with the nascent blood-based biomarkers for PD [56] and HD [57].

Intranasal Rifampin Delivery to the Brain

Employing intranasal delivery, notwithstanding its proximal location to the brain, still presents challenges and a review of pertinent anatomy is warranted. The nasal cavity is divided into halves by the nasal septum; each half has three regions; nasal vestibule, respiratory region and olfactory region. The nasal vestibule is the entrance to the nose and the respiratory region which contains nasal turbinates that warm and humidify incoming air. The olfactory region is situated at the roof of the nasal cavity and a full 7 cm from the nostrils. This uppermost region is the target area for olfactory delivery. The olfactory epithelium lines the olfactory region and contains elements of the olfactory nerve [58]. The respective areas of the nasal cavity are innervated by the olfactory nerve (CN I) and the trigeminal nerve (CN V). The olfactory neurons project through the surrounding olfactory epithelium and the cribriform plate then synapse at the olfactory bulb in the brain. While the trigeminal neuronal endings are not directly exposed to the respiratory epithelium of the nasal cavity, olfactory neurons are within the olfactory epithelium and reach directly into the nasal cavity. This anatomic difference is the reason why the smaller olfactory nerve, along with its perineuronal spaces, is the primary route for intranasal transport of substances to the brain [59].

Rifampin appears to have a pleiotropic effect on the main gatekeeper of substance transport, the permeability glycoprotein, P-gp.

A primary difficulty in treating CNS disease is the poor brain penetration of systemically administered therapeutic agents. This limitation is due to the makeup of the blood brain barrier (BBB); consisting of endothelial cells with tight junctions, it limits substrate permeability [60]. This anatomic cerebral protection from unwanted substrates is augmented by the presence of P-gp and its action as an efflux pump. In the setting of the BBB, rifampin is a strong inducer of P-gp and, as such, enhances the clearance of amyloid from the brain [30].

P-gp is also expressed in normal human nasal mucosa localized to both the olfactory epithelium and the endothelial cells surrounding the olfactory bulb - the nose-brain intersection. In this setting rifampin inhibits P-gp-mediated efflux and does so in a dose dependent manner facilitating CNS exposure [61].

There are increasing numbers of CNS acting pharmacologic agents that are delivered intranasally. These include treatments for seizure, migraine, major depressive disorder, subarachnoid hemorrhage and hypoglycemia. The complex structure of the nose and need to deliver the treatment to the olfactory epithelium has presented challenges [62]. Assorted strategies have been developed to address the need to deliver the drug to the olfactory epithelium. This includes nebulizers, gas propellants, excipients and breath powered devices [63–66].

“Bi-Directional” Intranasal Delivery to the Brain

Bi-directional intranasal delivery is a simple, effective, physiologic and no-cost alternative to the other intranasal delivery methods [67–71]. With normal bilateral inhalation, a metered pulse of spray is delivered to one or both nostrils. In contrast, with bi-directional delivery, the metered pulse flows

from one nostril to the end of the nasopharynx, turns around into the contralateral nasal cavity and exits through that contralateral nostril. This is accomplished by occluding the side that received the pulse and “blowing” [72]. Moreover, nasal dilation with phenylephrine aids delivery to the olfactory region - with unilateral delivery, dilation enhanced olfactory deposition by a factor of 2.2 and with bi-directional delivery dilation increased olfactory deposition 4-fold [73].

Conclusion

This article proposes the use of a well-known antibiotic drug, rifampin, repurposed to act against aberrant protein aggregations that are the pathologic representations of Alzheimer’s disease, Parkinson disease, Lewy body dementia, multiple system atrophy, Huntington disease and amyotrophic lateral sclerosis/frontotemporal dementia spectrum.

What are the actions of rifampin upon the aberrant proteins of these proteinopathies? Parsimoniously, rifampin is a gatekeeper and a housekeeper. Intranasal rifampin ushers itself into the CNS, disaggregates toxic proteins and escorts those proteins out. Rifampin is inexpensive, the standard rifampin metered nose spray prepared by a compounding pharmacy costs about \$145 dollars for 30ml [74]. Using 4 mg (1 mg/0.1ml) daily in a bi-directional manner, the preparation contains more than two months of daily rifampin treatment. Due to the current absence of disease modifying therapy for the age-related neurodegenerative proteinopathies, rifampin represents a reasonable, inexpensive therapeutic prospect for intervention against this diverse set of diseases.

Author Contributions: CTD chose the topic, both authors contributed equally to the research, preparation and review of the manuscript. All authors read and approved the final submission.

Conflict of Interests: The authors declare no competing interests.

Abbreviations

AD- Alzheimer’s disease, PD- Parkinson’s disease, LBD- Lewy body dementia, MSA- Multiple System Atrophy, HD- Huntington disease, ALS-FTD- amyotrophic lateral sclerosis/frontotemporal dementia spectrum, BBB- blood brain barrier, P-gp- permeability glycoprotein, TDP-43- transactive DNA-binding protein 43, CSF- cerebral spinal fluid, CN I- cranial nerve one (olfactory), CN V- cranial nerve five (trigeminal), SADAScog- Standardized Alzheimer's Disease Assessment Scale cognitive subscale, MIC- minimal inhibitory concentration.

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