Review Article

Therapeutic role of rifampicin in Alzheimer's disease

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Rifampicin exerts significant brain protective functions in multiple experimental models. Here we summarize the underlying mechanisms of the neuroprotective and pro-cognitive effects of rifampicin that are mediated by its anti-inflammatory, anti-tau, anti-amyloid, and cholinergic effects. Beyond suggesting that rifampicin shows strong brain protective effects in preclinical models of Alzheimer's disease, we also provide substantial clinical evidence for the neuroprotective and pro-cognitive effects of rifampicin. Future neuroimaging studies combined with clinical assessment scores are the following steps to be taken in this field of research.

Key words: Alzheimer's disease, amyloid beta clearance, neuroprotection, oligomeric amyloid hypothesis, rifampicin.

ALZHEIMER'S DISEASE (AD) IS the most important cause of a progressive decline of cognitive and memory functions among older people. It is a progressive neurodegenerative disease and ultimately leads to disturbance of memory and cognitive function, finally resulting in dementia.[1] Clinically, there are different stages of dementia that typically progress slowly from mild (early) to severe (late stage).[1] It is important to note that neurodegenerative changes in the affected regions of the Alzheimer's brain begin years before any signs of the disease are prominent. This latent period, which can last for years, is called preclinical AD, representing the target for any neuroprotective/neuropreventive approach. A therapeutic approach effectively blocking this neurodegenerative cascade would show huge benefits in the progress of this disease. The research of recent years has led to an improved precision in detection of early forms of AD by various metabolic measurements, such as glucose positron emission tomography (PET) and amyloid PET.

In this respect, improvement of early stage diagnosis has shifted focus more and more towards protection of neuronal cell populations in this early period of neurodegeneration. Although the classical 'time is brain' concept of stroke cannot be generalized to the relatively slow neurodegenerative nature of AD, it is important to note that early intervention in the critical period involving a preventive approach would provide important benefits. In this context, it has already been shown that early molecular interactions guided by early onset of neuroinflammation play an important role in the progress of AD.[2–5] Considering all these factors, it is not unreasonable to assume that there are some basic pathophysiological similarities between acute stroke and the early period of AD. In connection with this, an acute therapeutic approach similar to the *fibrin* dissolving therapy in stroke can also be considered for the early period of AD, which is characterized with accumulated amyloid *fibrils*. Accordingly, recent studies have revealed that the microglia-driven oxidative pathway modulates the amyloid beta (Aß) metabolism through the key mediators of neuroinflammation during AD.[3–5]

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In contrast to the conventional Aß concept, the alternative oligomeric amyloid hypothesis, which is closely linked to early neuroinflammation, enables us to investigate the acute/subacute neuroprotective effect of some anti-inflammatory and anti-oxidant drugs that have already been shown to be neuroprotective in cerebrovascular diseases.[6,7] Regarding this, antibiotics were demonstrated to counteract these processes, reduce reperfusion failure, free radical formation, and ultimately reduce ischemic damage.[6,7]

Rifampicin is one of several neuroprotective antibiotics that may simultaneously modulate the neuroinflammatory response and Aß metabolism in AD.[6] Our argument to involve rifampicin is that it combines an anti-inflammatory and anti-oxidative property that is capable of crossing the blood–brain barrier (BBB) with neuroprotective properties that help by limiting inflammation and oxidative stress. However, despite considerable literature on the neuroprotective effect of rifampicin, there are limited and controversial data on the therapeutic role of rifampicin in AD. This might be due to the lack of understanding of pathophysiological underpinnings of AD. Notably, there is a growing body of pathophysiological evidence suggesting that there is cross talk between amyloid metabolism, free radical injury, and neuroinflammation. In light of these findings, we aimed to provide an update on the neuroprotective role of rifampicin in AD. Beyond summarizing the conventional and alternative amyloid hypothesis, we have also evaluated the most significant Aß clearance mechanisms that may play an important role in mediating the neuroprotective role of rifampicin in AD. To that end, we have been focused on the AD-relevant anti-inflammatory, anti-oxidant, anti-amyloidogenic effects of rifampicin.

CONVENTIONAL AMYLOID HYPOTHESIS

The neuropathological feature of AD is defined as the accumulation of extracellular senile plaques and intracellular neurofibrillary tangles associated with significant neuronal cell death and related brain atrophy.[8–11] It has been shown that the complex enzymatic cleavage of transmembrane amyloid-precursor protein (APP) leads to the generation of Aß from APP.[12,13] Moreover, in a healthy brain, the clearance of the amyloid load is critical for the maintenance of normal brain function while the disturbance in the balance between protein fragment production and its clearance[12,13] may result in amyloid accumulation closely linked to free radical production.[14,15] This suggests that in addition to amyloid accumulation, inflammation and oxidative injury play major roles in AD pathogenesis. In this respect, the latest research suggests that micromolar concentrations of Aß in contrast to picomolar concentrations within the brain cause neurotoxicity and subsequent neurodegeneration.[2,14] During this phase, it has already been demonstrated that microglia-driven inflammatory response that is due to Aß aggregation increases over time as the disease progresses.[2,15] These findings suggest that there is a cross talk between the amyloid and tau-related neurotoxicity and neuroinflammation.

EARLY INFLAMMATION AND OLIGOMERIC AMYLOID HYPOTHESIS: A NEW CROSS TALK?

In contrast to the conventional Aß cascade hypothesis, which plays a critical role in sustaining neuroinflammation in the later and chronic stages, the oligomeric amyloid hypothesis proposes that toxic amyloid oligomers may trigger glial activation in the early stages of inflammation.[16,17] Based on these findings, it is not unreasonable to assume that cognitive dysfunction, beginning early in the disease, can be attributed to oligomer-induced disruption of synaptic plasticity at its earliest, which is followed by oligomer-induced neuronal degeneration with later stages. These Aß oligomers ranging from dimers to higher polymers have been identified in AD brain extracts while experimental studies indicate that these oligomers may impair excitatory synapses through a receptor complex involving mGluR5 and NMDA receptors leading to specific synaptic dysfunction, which also includes the inhibition of LTP.[16–19] More generally, it has already been revealed that Aβ oligomers initiate several neuropathological processes involving the axonal dysfunction, tau hyperphosphorylation, dysregulation of Ca^{2+} homeostasis, oxidative stress, mitochondrial damage, energy depletion, endoplasmic reticular stress, proteasome inhibition, cell cycle re-entry, activation astrocytes, and microglia, which are characterized by prominent neuroinflammation and directly correlate to brain dysfunction in AD.[16] Taken together, based on its critical role for early neuroinflammatory response and related neuronal dysfunction through microglial activation and increased

levels of inflammatory markers (i.e., inducible nitric oxide, nitric oxide, and tumor necrosis factor-α),[17] it can be hypothesized that early memory loss in AD can be reversed with feasible anti-inflammatory, anti-oligomeric, and neuroprotective agents, such as rifampicin. Thus, studies have already revealed that rifampicin inhibits Aß oligomerization to produce monomeric components that form less toxic insoluble fibrils.

ROLE OF PERMEABILITY GLYCOPROTEIN AND LIPOPROTEIN RECEPTOR-RELATED PROTEIN-1 TRANSPORTERS AND BBB CLEARANCE MECHANISMS IN AD

Aβ-peptide is at the center of the disease pathogenesis and is responsible for the generation of amyloid plaques through proteolytic cleavage by β- and γ-secretases[20–23] which are important neuropathological hallmarks of AD[20–23] Depending on the cleavage site by γ-secretase, $A\beta_{40}$ and $A\beta_{42}$ differ not only in their length but also in their production and cleavage rate.[24] During this process, $A\beta_{40}$ is produced at a significantly greater rate than $A\beta_{42}$, while the critical point for the neurodegenerative process is determined by the final levels of free Aβ, which is related to the balance between generation, aggregation, degradation, and clearance from the brain.[20–24] The final concentrations of Aβ also showed a significant correlation with synaptic pathology and the presence of dementia.[22] Recent evidence indicates that disturbed clearance of Aβ from the brain also plays an important role in sporadic and familial forms of AD.[25,26] The homeostasis of Aβ is critically dependent on its clearance, indicating that sufficient amounts of Aβ should be eliminated from the brain to maintain the critical balance between the production and clearance of Aβ proteins. Accordingly, recent studies also suggest that the endocytic elimination via transmembrane protein lipoprotein receptor-related protein-1 plays an important role in the clearance of Aβ from the brain. It has already been demonstrated that low- density lipoprotein receptor-related protein 1 (LRP1) reveals a diverse modifying effect on amyloid trafficking in the brain.[27,28] Additionally, the efflux transporter permeability glycoprotein (P-gp), which is located on brain capillary endothelial cells in the BBB and belongs to the adenosine-triphosphate-binding cassette B1 transporter family contributes to the elimination of $A\beta_{1-40}$ and $A\beta_{1-42}$ from the brain across the BBB.[29–32] In agreement with this, recent evidence suggests that decreased transport activity of P-gp is associated with increased levels of Aβ in aged humans and in the specific brain regions affected in AD patients.[29] These findings together suggest the important role of Aß transport across the BBB in the pathogenesis of AD.

THE NEUROPROTECTIVE EFFECT OF RIFAMPICIN IN AD

Preclinical studies

Rifampicin is a broad-spectrum antibiotic and belongs to the fermentation products of *Nocardia mediterranei*.[4–6,33–35] Rifampicin consists of a naphtho-hydroquinone chromophore spanned by a lipophilic aliphatic ansa chain[33] (Fig. 1[36]) that is mainly responsible for the transport of the drug across the BBB into the brain parenchyma.[34,35] Rifampicin reaches maximal serum concentration 1–4 h after application and its plasma half-time is 2–5 h.[34,35] Beyond its conventional anti-infectious effect, rifampicin also exerts significant neuroprotective effect in various experimental studies. The neuroprotective effect of rifampicin has already been shown in various neurodegenerative diseases, including Parkinson's disease and multisystem atrophy. The underlying mechanism of action includes increased dopaminergic cell survival, decreased alpha synuclein toxicity, and MPP+-induced

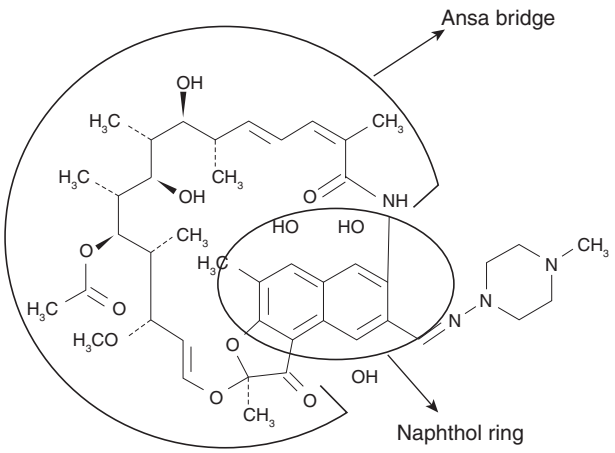

Figure 1. Structural formula of rifampicin, including the ansa bridge and naphthol ring, with oxygen atoms and hydroxyls (modified from Campbell *et al.*[36] with permission).

apoptosis, which are associated with the stabilization of the mitochondrial and endoplasmic reticular stress via modulation of critical cytoprotective chaperon and anti-apoptotic proteins (i.e., glucose-regulated protein 78 and Bcl-2).[37–42] Moreover, there is rapidly replicating evidence showing that rifampicin may attenuate the free radical injury and decrease the neuroinflammation that finally result with significant neuroprotective effect.[43] For instance, a recent study indicated that rifampicin may decrease toll-like receptor 2 (TLR2) and mitogen-activated protein kinases (MAPK) via suppressing the nuclear factor-kappa B, which may support the potential anti-inflammatory role of rifampicin in Parkinson's disease.[42,44,45]

Considering all this valuable evidence, we preferred to summarize the neuroprotective mechanisms of rifampicin (Fig. 2) that are most relevant to the pathogenesis of AD. These include its inhibitory activity on free oxygen radicals, tau and Aβ protein accumulation, microglial activation, apoptotic cascades, and its most recently defined stimulating effect on brain Aß clearance through LRP1 and P-gp.

It has already been shown that free radical production plays an important role in the generation of Aß.[14,15] Accordingly, studies have revealed the therapeutic role of antioxidative agents in Aß-plaque-related neurotoxicity in AD. The first *in vitro* study was conducted by Tomiyama *et al.*, who demonstrated that rifampicin inhibited aggregation and fibril formation of synthetic $A\beta_{1-40}$ peptide and prevented neurotoxicity in a dose-dependent manner in rat pheochromocytoma PC12 cells.[46] The authors used the electron spin resonance technique combined with a cytotoxicity assay and demonstrated that rifampicin revealed significant anti-oxidative effects via its naphtho-hydroquinone (or naphthoquinone) ring while the main responsible anti-scavenger (hydroxyl radical scavenger) activity was attributed to the hydroxyl group at position C-1 of the naphtho-hydroquinone.[33] Interestingly, those authors also demonstrated that rifampicin was 10–100-fold more effective than vitamins in inhibiting Aß aggregation. Another study also showed that the ansa chain of rifampicin was not essential for the Aß aggregation inhibitory activities while its lipophilicity contributed significantly to transport of the drug molecule into the brain *in vivo*.[35] The majority of *in vitro* studies confirmed the anti-amyloid effect of rifampin, including inhibition of amyloid fibril formation.[47,48] These findings together suggest that both the rifampicin-mediated inhibition of Aß aggregation and its free radical scavenging effects could be essential for the therapeutic role of rifampicin in AD. These study results are in agreement with previous findings, suggesting that the anti-amyloid effect of rifampicin includes radical-scavenging activity associated with decreased peptide aggregation, amyloid-binding, and amyloid–cell interaction. Interestingly, further studies evaluating the anti-amyloid effect of rifampicin on amylin fibrin aggregation and related toxicity have revealed that the inhibitory effect was induced by their binding to peptide fibrils rather than by their intracellular antioxidant action.[49–51] These study results suggested the presence of an additional mechanism, other than

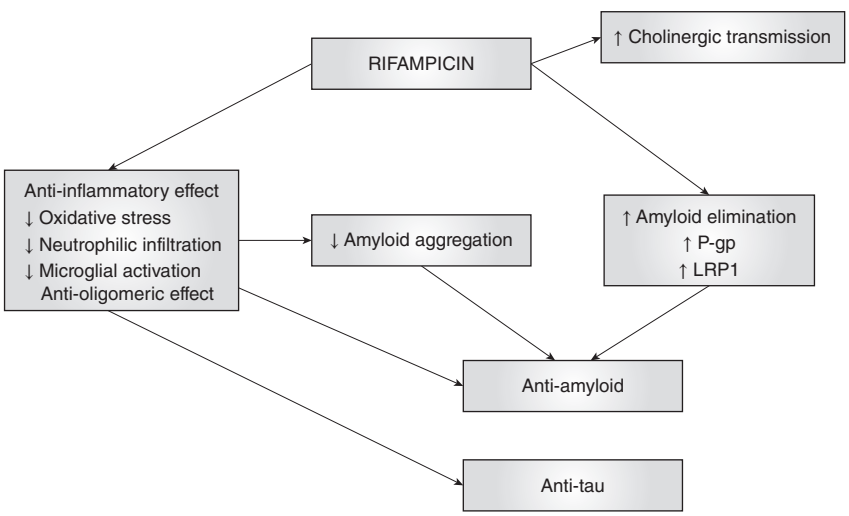

Figure 2. The underlying mechanisms of the neuroprotective role of rifampicin in Alzheimer's disease.

scavenging of free radicals, by which rifampicin and its analogs may decrease the Aß toxicity. These preclinical data were confirmed by Lieu *et al.*,[49] who demonstrated that rifampicin inhibited amyloid fibrillogenesis of lysozyme in a concentration-dependent manner utilizing a hen egg-white lysozyme model, which is a protein-unfolding model that is widely used in crystallography. The subsequent cell culture studies using fluorescence spectrometric analysis showed that rifampicin displayed significant anti-oxidant and anti-amyloid activity, including the inhibition of preformed fibril accumulation.[49,51] In their molecular-based neuropreventive study for AD, Umeda *et al.* have very recently revealed that rifampicin conferred significant activity against the accumulation of Aß and tau oligomers in various transgenic mice models.[52] The administration of rifampicin for 1 month resulted in significant decrease in amyloid and tau toxicity associated with improved synapse loss and microglial activation. Moreover, rifampicin also improved memory loss and inhibited apoptotic cascades, including the caspase 3 activation and cytochrome c release in the hippocampus.[52] Furthermore, those authors also revealed that rifampicin stimulated the restoration of autophagy-lysosomal function. Although there were some minor differences in amyloid deposition in the different transgenic mice models (i.e., tauopathy, amyloid oligomer, and AD model) used in this study, the results indicated that rifampicin exerted significant inhibitor activity on tau and amyloid oligomer accumulation, tau hyperphosphorylation, microglial activation, and apoptotic cascades, which were positively correlated to the neurocognitive outcomes.[52] These findings together suggest a potential role of rifampicin as a neuroprotective agent but also as an effective neuropreventive agent in Alzheimer's and other neurodegenerative diseases.

From another point of view, recent evidence strongly suggests that impaired clearance of Aß across the BBB might lead to the formation of Aß brain deposits and AD progression.[53–55] The efflux transporter P-gp may play an important role in the elimination of $A\beta_{1-40}$ and $A\beta_{1-42}$ from the brain across the BBB.[53–55] In agreement with this, further studies have demonstrated that decreased intracellular accumulation of A1–40 is associated with P-gp upregulation caused by rifampicin[56,57] These findings are consistent with the correlation between *in vitro* concentration-dependent increase in P-gp expression and activity by rifampicin.[58] Moreover, a very recent mice study has shown that the upregulation of low-density LRP1 and P-gp at the BBB by rifampicin and caffeine enhanced brain amyloid clearance.[59] This suggested the presence of a possible transporter/receptor that plays an important role in amyloid clearance, which is upregulated by rifampicin.[60] Accordingly, a very recent study by Kaur *et al.* has revealed that rifampicin significantly improved memory dysfunction and locomotor impairment in a rat dementia model.[61] By evaluating the underlying mechanisms of neuroprotection, they have interestingly shown that rifampicin significantly reduced the oxidative stress, neutrophilic infiltration, amyloid deposition, and acetylcholinesterase activity that was reversed with the inhibition of Pregnane X receptors (PXR), which mediate the upregulation of P-gp expression. Beyond suggesting the anti-oxidative, anti-inflammatory, and amyloid-lowering effects of rifampicin, this study also indicated that rifampicin could enhance cholinergic neurotransmission through its anti-cholinesterase activity. Additionally, rifampicin's recently defined agonist activity on PXR may provide further rationale for the potential role of PXR in mediating the procognitive and neuroprotective effect of rifampicin in the pathophysiology of AD.

It should also be noted that there are very rare *in vitro* studies indicating that rifampicin does not inhibit Aß protein aggregation and neurotoxicity in pancreatic islet cells and cerebral cortical neurons.[62,63] Despite these conflicting *in vitro* data, there are rapidly replicating *in vivo* and *in vitro* studies that are supporting a possible relation between P-gp dysregulation and cognitive improvement in patients with AD. These findings together indicate that in addition to oxidative injury and fibril aggregation, targeting the expression of P-gp by rifampicin could be an effective strategy in decreasing the progression of AD.

Clinical studies

In contrast to the preclinical data, only a few clinical studies have evaluated the effects of rifampicin in patients with AD regarding efficacy and outcome. Namba *et al.* examined 16 brains from leprosy patients without dementia and compared the neurofibrillary tangles and senile plaques in 140 Japanese non-demented elderly subjects through immunohistochemical staining.[64] Interestingly they have reported that non-demented elderly leprosy patients

who were on rifampicin treatment for years showed an unusual absence of senile plaques in their brains compared with age-matched controls.[64] Surprisingly, these results could not be replicated with the following work showing that rifampicin does not affect the prevalence of AD in leprosy patients.[62] Subsequent studies that were designed to understand the causal antidementia effect of rifampicin also failed to provide clear clinical data. Loeb *et al*. have confirmed the anti-dementia effects of oral rifampicin (300 mg/daily for 3 months) resulting in a significant increase in cognitive function in 101 mild–moderate AD patients measured by a Standardized Alzheimer's Disease Assessment Scale – Cognitive Subscale score.[65] Unfortunately, these promising data could not be confirmed in a study that included a 12-month rifampicin treatment.[66] In this study, short-term treatment effect might have been overruled by a lack of long-term treatment effect of rifampicin.

In line with this, Iizuka *et al*. described that preventive effect of rifampicin needs at least 450 mg daily for 1 year even during the pre-dementia stage.[67] In their interesting retrospective FDG-PET study, rifampicin therapy in the predementia stage significantly improved the metabolic (posterior cingulate gyrus) and cognitive decline in the long-term follow up. Rifampicin dose and treatment (450 mg/day for ≥12 months) significantly improved the FDG uptake in the posterior cingulate gyrus, which was reflected in Mini-Mental State Examination scores. These findings together suggested that the failure in clinical trials with rifampicin is probably due to the late timing and insufficient dosage of the treatment and indicate the importance of higher doses and longer treatment duration of preventive treatment. In this respect, adverse events (i.e., drug resistance and gastrointestinal side-effects) associated with long-term use can easily be overcome with combined antibiotic treatment strategy and quick dose adjustment due to the short half-life of rifampicin. Moreover, it should also be remembered that different clinical study designs, as well as some well-known systematic translation failures of preclinical findings into the human situation, could be responsible for inconsistent clinical results.

CONCLUSION

Besides its anti-infectious properties, rifampicin also exerts strong brain protective effects in various models of neurodegeneration and brain trauma. Furthermore, pilot clinical studies indicate that patients with AD may benefit from rifampicin treatment. Despite these positive study results, clinical confirmatory evidence remains scarce and results are inconsistent.[61–67] To overcome the above-mentioned barriers to consistent clinical data, well-designed randomized clinical research with larger experimental pharmacological combination studies is needed. This approach should also be combined with prospective functional neuroimaging data (etc., amyloid-PET) and clinical assessment scores. This multimodal strategy would help us to enlighten the clinical relevance of the neuroprotective effect of rifampicin, which may also offer a significantly low-cost alternative to the long-duration of expensive antidementia treatment, especially in third-world countries.

DISCLOSURE STATEMENT

There is no conflict of interest in this study.

AUTHOR CONTRIBUTIONS

B.Y.: Conception and design of the study; acquisition and analysis of data. L.H.: Drafting the manuscript and figures. M.O.: Drafting the manuscript. U.K.: Acquisition and analysis of data; drafting the figures. E.K.: Acquisition and analysis of data; drafting the manuscript. W.R.S.: Conception and design of the study; acquisition and analysis of data; drafting the manuscript.

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