Inhibition of Amyloid β Protein Aggregation and Neurotoxicity by Rifampicin

ITS POSSIBLE FUNCTION AS A HYDROXYL RADICAL SCAVENGER*

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Aggregation of physiologically produced soluble amyloid β protein (Aβ) to insoluble, neurotoxic fibrils is a crucial step in the pathogenesis of Alzheimer's disease. Aggregation studies with synthetic Aβ1-40 peptide by the thioflavin T fluorescence assay and electron microscopy and cytotoxicity assays using rat pheochromocytoma PC12 cells showed that an antibiotic, rifampicin, and its derivatives, which possess a naphthohydroquinone or naphthoquinone structure, inhibited Aβ1-40 aggregation and neurotoxicity in a concentration-dependent manner. Hydroquinone, p-benzoquinone, and 1,4-dihydroxynaphthalene, which represent partial structures of the aromatic chromophore of rifampicin derivatives, also inhibited Aβ1-40 aggregation and neurotoxicity at comparable molar concentrations to rifampicin. Electron spin resonance spectrometric analysis revealed that the inhibitory activities of these agents correlated with their radical-scavenging ability on hydroxyl free radical, which was shown to be generated in cell-free incubation of Aβ1-40 peptide. These results suggest that at least one mechanism of rifampicin-mediated inhibition of Aβ aggregation and neurotoxicity involves scavenging of free radicals and that rifampicin and/or appropriate hydroxyl radical scavengers may have therapeutic potential for Alzheimer's disease.

Amyloid β protein (Aβ), a 39–43 amino acid peptide, is a primary component of the amyloid that is deposited in the brains of patients with Alzheimer's disease (AD). Aβ is physiologically produced as a soluble form by enzymatic cleavage of the larger precursor, termed amyloid precursor protein (1–3). Soluble Aβ is not toxic and its physiological function is not known; however, it has been shown that aggregation of Aβ to insoluble fibrils causes neurotoxic change of the peptide (4–6). Therefore, inhibition of this process would seem to be an effective therapeutic strategy for AD.

The mechanisms of Aβ aggregation and neurotoxicity are not completely known. Recently, it was suggested that free radical generation may be involved in the processes of Aβ aggregation and/or neurotoxicity (7–9). Those hypotheses imply that appropriate radical scavengers could inhibit Aβ aggregation and/or neurotoxicity.

It was previously reported that non-demented elderly leprosy patients showed an unusual absence of senile plaques in their brains compared with age-matched controls (10). Although that finding itself is still a matter of controversy (11), we surmised that some drug being used for leprosy might be preventing Aβ aggregation, resulting in the absence of amyloid deposition. Thus, we tested two well known anti-leprosy drugs, dapsone and rifampicin, and found that rifampicin inhibited Aβ1-40 aggregation and neurotoxicity in vitro (12). Rifampicin is a semisynthetic derivative of the rifamycins, a class of antibiotics that are fermentation products of Nocardia mediterranei (for a review, see Ref. 13). The common structure of rifamycins is a naphthohydroquinone or naphthoquinone chromophore spanned by an aliphatic ansa chain. Taken together with the above free radical hypotheses, this structural feature of rifampicin suggests that this drug may function as a radical scavenger with its naphthohydroquinone ring in inhibiting Aβ aggregation and neurotoxicity.

In the present study, we confirmed the published finding that free radicals are generated in cell-free incubation of Aβ1-40 peptide (7) and show that at least the hydroxyl radical is involved in this process. Also, we show that the inhibitory activities of rifampicin and its derivatives against Aβ aggregation and neurotoxicity correlate with their radical-scavenging ability on hydroxyl radical, which function arises from their naphthohydroquinone or naphthoquinone structure. These results implicate therapeutic potential of rifampicin for AD and provide useful information for developing new compounds for the treatment of AD.

MATERIALS AND METHODS

Agents and Peptides—Rifampicin and rifamycin SV are commercially available (Sigma), while other rifampicin derivatives were synthesized from rifamycin SV in our laboratory according to the methods of Kump and Chen (U.S. Patent 5 003 070, 1991), which are summarized in Fig. 1. All other agents were obtained from Tokyo Kasei Kogyo Co. (Japan), but three natural radical scavengers (a-tocopherol, ascorbic acid, and β-carotene) were purchased from Sigma. Aβ1-40 peptide was synthesized by ordinary solid-phase methods with FMoc (N-(9-fluorenyl) methoxycarbonyl) amino acids (Applied Biosystems Inc.) using a 431A peptide synthesizer (Applied Biosystems Inc.) and purified by reverse-phase high performance liquid chromatography using a Cosmosil 5C4-AR-300 column (Nacalai Tesque Inc., Japan).

Aggregation Studies—Peptide aggregation was measured by the thioflavin T (ThT) fluorescence assay, in which the fluorescence intensity reflects the degree of aggregation (14). All agents to be tested were dissolved in dimethyl sulfoxide (Me2SO) at various concentrations. The solubility of β-carotene in Me2SO was very low, so suspensions of β-carotene were used. The Aβ1-40 peptide was solubilized in double deionized water at a concentration of 40 μM and dispensed into Eppendorf tubes (50 μl/tube). One μl of each test agent solution was added to the tubes in triplicate, and then the peptide solutions were mixed with an equal volume of 2 × phosphate-buffered saline solution. Control peptide solutions containing 1% Me2SO without any test agent were used.
also prepared. The solutions were incubated at 37°C for 7 days, and then the ThT fluorescence assay was performed using a FP-770 spectrofluorometer (Jasco, Japan), as described previously (12). Fibril formation by Aβ1–40 peptide was also examined by electron microscopy using a H-7100 electron microscope (Hitachi, Japan), as described previously (12). No bacterial contamination was observed in the peptide solutions even after a 7-day incubation.

Cytotoxicity Assays—The cytotoxic effects of Aβ were assessed by 3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide (MTT) reduction with rat pheochromocytoma PC12 cells (15). The PC12 cells were prepared as described previously (12). The peptide solutions incubated with each test agent for 7 days were added to the cell culture at a final peptide concentration of 2 μM. After a 2-day incubation, the MTT assay was performed as described previously (15).

Electron Spin Resonance (ESR) Spectrometry—The Aβ1–40 peptide was dissolved in double deionized water to a concentration of 1 mg/ml in the presence of 50 mM N-tert-butylnaphthyl nitronitrone (PBN) (Sigma). One of the solutions was mixed with a 1:10 volume of Me6SO. The solutions were transferred into 75-μl aqueous quartz ESR flat cells and incubated at room temperature. After various incubation times, the ESR spectra were determined using a JEOL FE2XG ESR spectrometer (JEOL, Japan) under conditions of a magnetic field of 329.0 ± 5 millitesla, a magnetic power of 20 milliwatts, 9.225 GHz, a response of 1 s, a temperature of 25°C, an amplitude of 5,000, a sweep time of 16 min, and a modulation of 100 kHz × 0.08 millitesla. To evaluate the radical-quenching ability of agents, the hydroxyl radical generated by the Fenton reaction (16) was used. All agents to be tested were dissolved in acetonitrile at various concentrations. One-hundred microliters of 2 mM FeSO4 solution was dispensed into Eppendorf tubes, and then 20 μl of agent, 100 μl of 2 mM H2O2, and 2 μl of 5 mM 5,5-dimethyl-1-pyrroline-N-oxide (DMPO) (Aldrich) were sequentially added to the tubes. The ESR spectra were determined at 3 min after the addition of DMPO under the same conditions as described above, except for using an amplitude of 1,000 and a sweep time of 4 min.

RESULTS
To identify the structure required for the inhibitory activities of rifampicin, we synthesized a panel of rifampicin derivatives (Fig. 1) and tested them for effects on Aβ1–40 aggregation and neurotoxicity (Table I). Fig. 2 shows the time course of aggregation of Aβ1–40 peptide without any test agent. Rifampicin inhibited Aβ aggregation and neurotoxicity in a concentration-dependent manner. This inhibitory effect of rifampicin against Aβ aggregation was confirmed by electron microscopy (Table I and Fig. 3). A control peptide solution showed apparent amyloid-like fibrils of Aβ1–40, while very few fibrils were observed in the presence of 100 μM rifampicin. Rifamycin SV and rifampicin S, which possess a naphthohydroquinone and naphthoquinone ring, respectively, also inhibited Aβ aggregation and neurotoxicity, without any functional group at position C-3 of their aromatic ring. From these observations and the free radical hypotheses (7–9), we speculated that the active structure of rifampicin responsible for the inhibition of Aβ’s activities might be the naphthohydroquinone (or naphthoquinone) ring. In support of this, hydroquinone, p-benzoquinone, and 1,4-dihydroxynaphthalene, which represent partial structures of the aromatic chromophore of rifampicin derivatives, inhibited Aβ aggregation and neurotoxicity at comparable molar concentrations to rifampicin. The hydroxyl group at position C-1 of the naphthohydroquinone ring must be essential for the inhibitory
against rifampicin (13), were not necessary for the inhibitory activities and sanchain, which are essential for the antibacterial activity of the hydroxyl group at position C-8 and the double bonds of the equally required for the inhibitory activities. On the contrary, that both of the hydroxyl groups at positions C-1 and C-4 are demonstrated with RFM-007 and RFM-008, respectively. In addition, activities of rifampicin, because substitution of the hydroxyl group at this position, or cyclization between the hydroxyl group at position C-1 and the carbon at position C-15 of the ansa chain, considerably reduced the activities, as demonstrated with RFM-007 and RFM-008, respectively. In addition, p-methoxyphenol also showed only weak inhibition, suggesting that both of the hydroxyl groups at positions C-1 and C-4 are equally required for the inhibitory activities. On the contrary, the hydroxyl group at position C-8 and the double bonds of the ansa chain, which are essential for the antibacterial activity of rifampicin (13), were not necessary for the inhibitory activities against Ab aggregation and neurotoxicity, as shown with RFM-005 and RFM-030, respectively. As well, the functional group at position C-3, which modulates the antibacterial activity of rifampicin probably by influencing transport of the drug molecule through the bacterial wall and membrane (13), appeared not to affect the anti-Ab activities, as shown with rifamycin SV and RFM-002. Thus, we concluded that the inhibitory activities of rifampicin against Ab aggregation and neurotoxicity arise from its naphthohydroquinone (or naphthoquinone) structure. As a reference for evaluating the activity of rifampicin, three natural radical scavengers, a-tocopherol (vitamin E), ascorbic acid (vitamin C), and p-carotene (provitamin A), were also examined. These vitamins were all effective in inhibiting Ab aggregation, but their activities were weaker than that of rifampicin. Thus, 10–100-fold higher concentrations were necessary for the vitamins to achieve the same degree of inhibition of Ab aggregation as shown by rifampicin.

As mentioned already, the naphthohydroquinone (or naphthoquinone) structure of rifampicin is speculated to function as a radical scavenger. Thus, using ESR spectrometry, we examined the ability of rifampicin and the related agents to quench free radicals (Fig. 4). Initially we confirmed the published finding that free radicals are generated in cell-free incubation of Ab 1-40 peptide (7). With PBN as a spin trapping agent, an Ab 1-40 solution showed an obvious three-line spectrum (\(\alpha_H = 17.1 \text{ G} \)) after 3-day incubation. When the peptide was incubated in the presence of MeSO, it showed a different ESR

### Table I

Effects of test agents on Ab 1-40 aggregation, cytotoxicity and fibril formation

| Agent         | Concentration | Tht fluorescence | MTT reduction | Fibrils |
|---------------|---------------|------------------|---------------|---------|
|               | \(\mu M\)     | % of MeSO control | % of control |         |
| MeSO          | -             | 100 \(\pm 10\)   | 51 \(\pm 4\) | +       |
| Rifampicin    | 10            | 7 \(\pm 1\)      | 92 \(\pm 2\) | -       |
|               | 1             | 77 \(\pm 9\)     | 59 \(\pm 1\) | -       |
| Rifamycin SV  | 100           | 1 \(\pm 1\)      | 98 \(\pm 2\) | -       |
|               | 10            | 32 \(\pm 13\)    | 66 \(\pm 1\) | -       |
| Rifamycin S   | 100           | 2 \(\pm 2\)      | 99 \(\pm 4\) | -       |
|               | 10            | 39 \(\pm 4\)     | 69 \(\pm 1\) | -       |
|               | 1             | 79 \(\pm 5\)     | 52 \(\pm 3\) | -       |
| RFM-002       | 100           | 5 \(\pm 1\)      | ND*           | ND      |
|               | 10            | 29 \(\pm 12\)    | ND*           | ND      |
|               | 1             | 81 \(\pm 16\)    | ND*           | ND      |
| RFM-005       | 100           | 5 \(\pm 1\)      | ND*           | ND      |
|               | 10            | 12 \(\pm 5\)     | ND*           | ND      |
|               | 1             | 54 \(\pm 8\)     | ND*           | ND      |
| RFM-007       | 100           | 52 \(\pm 3\)     | 69 \(\pm 3\) | +       |
|               | 10            | 65 \(\pm 12\)    | 56 \(\pm 2\) | -       |
|               | 1             | 103 \(\pm 24\)   | 56 \(\pm 2\) | -       |
| RFM-008       | 100           | 47 \(\pm 11\)    | 69 \(\pm 4\) | +       |
|               | 10            | 60 \(\pm 6\)     | 66 \(\pm 2\) | -       |
|               | 1             | 75 \(\pm 22\)    | 61 \(\pm 2\) | -       |
| RFM-030       | 100           | 0 \(\pm 1\)      | 101 \(\pm 9\) | -       |
|               | 10            | 38 \(\pm 20\)    | 75 \(\pm 2\) | -       |
| Hydroquinone  | 100           | \(-1 \(\pm 1\)\) | 102 \(\pm 3\) | -       |
|               | 10            | 9 \(\pm 3\)      | 57 \(\pm 4\) | -       |
|               | 1             | 44 \(\pm 5\)     | 51 \(\pm 2\) | -       |
| p-Benzoquinone| 100           | 1 \(\pm 2\)      | 104 \(\pm 6\) | -       |
|               | 10            | 5 \(\pm 0\)      | 54 \(\pm 3\) | -       |
|               | 1             | 62 \(\pm 6\)     | 51 \(\pm 1\) | -       |
| 1,4-Dihydroxynaphthalene | 100  | 4 \(\pm 1\)      | 90 \(\pm 9\) | -       |
|               | 10            | 15 \(\pm 3\)     | 51 \(\pm 1\) | -       |
|               | 1             | 46 \(\pm 18\)    | 58 \(\pm 3\) | -       |
| p-Methoxyphenol| 100        | 38 \(\pm 10\)    | 60 \(\pm 2\) | +       |
|               | 10            | 81 \(\pm 11\)    | 58 \(\pm 2\) | -       |
| a-Tocopherol  | 1000          | 28 \(\pm 11\)    | 79 \(\pm 2\) | ND      |
|               | 100           | 76 \(\pm 22\)    | 53 \(\pm 2\) | -       |
|               | 10            | 78 \(\pm 26\)    | 60 \(\pm 3\) | -       |
| Ascorbic acid | 1000          | 12 \(\pm 1\)     | 64 \(\pm 5\) | ND      |
|               | 100           | 72 \(\pm 12\)    | 50 \(\pm 2\) | -       |
|               | 10            | 75 \(\pm 9\)     | 50 \(\pm 2\) | -       |
| p-Carotene    | 1000          | 10 \(\pm 2\)     | 84 \(\pm 3\) | ND      |
|               | 100           | 16 \(\pm 1\)     | 49 \(\pm 3\) | -       |
|               | 10            | 61 \(\pm 22\)    | 66 \(\pm 4\) | -       |

*ND, not determined.*
spectrum \( (\alpha_0 = 17.2 \text{ G} \text{ and } \alpha_0 = 16.0 \text{ G}, \alpha_H = 3.5 \text{ G}) \) partly due to new species of free radicals. Since \( \text{Me}_2\text{SO} \) is known to react with the hydroxyl radical to produce the methyl radical (17), and actually, the ESR spectrum of hydroxyl radical in the presence of \( \text{Me}_2\text{SO} \) \( (\alpha_0 = 16.4 \text{ G}, \alpha_H = 3.6 \text{ G}) \) corresponded to some portion of the ESR spectrum of an \( \text{A}\beta1–40 \) solution containing \( \text{Me}_2\text{SO} \), the above ESR result suggests that at least the hydroxyl radical is involved in the radical-generating process in \( \text{A}\beta \) solution. Based on this observation and because of the simplicity of the radical-generating system, we focused our experiments on the radical-quenching ability of agents in relation to the hydroxyl radical generated by the Fenton reaction (16). With DMPO instead of PBN, a typical 1:2:2:1 four-line spectrum \( (\alpha_0 = \alpha_H = 14.9 \text{ G}) \) due to hydroxyl radical (18) was detected in the control solution. As expected from the molecular structure, rifampicin quenched the hydroxyl radical in a concentration-dependent manner. The two analogs, hydroquinone and 1,4-dihydroxynaphthalene, also diminished the hydroxyl radical, while RFM-008 and p-methoxyphenol showed no quenching ability at concentrations up to 1 mM. These results suggest that the inhibitory activities of the agents against \( \text{A}\beta \) aggregation and neurotoxicity correlate with their radical-quenching ability on hydroxyl radical and that at least one mechanism by which rifampicin and its analogs inhibit \( \text{A}\beta \) aggregation and neurotoxicity involves scavenging of free radicals.

**DISCUSSION**

Neuronal degeneration is a significant pathological feature of AD brains, and the toxicity of \( \text{A}\beta \) has been implicated in the neuronal damage. Although the molecular mechanisms of \( \text{A}\beta \) neurotoxicity are not completely known, there is general agreement that the neurotoxicity of \( \text{A}\beta \) correlates with its state of aggregation (4, 5). Furthermore, it was shown that fibril formation by \( \text{A}\beta \) is definitely necessary for its neurotoxicity (6). These observations suggest that drugs that inhibit \( \text{A}\beta \) aggregation may be able to protect neurons from \( \text{A}\beta \) toxicity and hence may have therapeutic potential for AD. Here we have shown that rifampicin and its derivatives, which inhibit \( \text{A}\beta \) aggregation, also inhibit \( \text{A}\beta \) neurotoxicity.

It was recently proposed that the \( \text{A}\beta1–40 \) peptide, in aqueous solution, spontaneously fragments into free radical peptides, which may react with one another to generate covalently bonded aggregates and may also attack nerve cell membranes to induce neuronal degeneration (7). We confirmed that free radicals are generated in cell-free incubation of \( \text{A}\beta1–40 \) peptide, and our findings that radical scavengers inhibit \( \text{A}\beta \) aggregation and neurotoxicity may support this hypothesis. However, the possibility cannot be ruled out that free radicals are generated independently of \( \text{A}\beta \) peptide and then trapped and stabilized by the peptide to be detected in ESR analysis. Oxidation of \( \text{A}\beta \) by free radicals was shown to cause peptide aggregation, which was prevented by radical scavengers (8).

It was also demonstrated that \( \text{A}\beta \) induces increased intracellular \( \text{H}_2\text{O}_2 \) accumulation, which may cause oxidative damage on neurons probably via hydroxyl radical generation (9). A number of antioxidants and the \( \text{H}_2\text{O}_2 \)-degrading enzyme, catalase, protected cells from \( \text{H}_2\text{O}_2 \) accumulation and also \( \text{A}\beta \) neurotoxicity (9). Our findings that hydroxyl radical scavengers inhibited \( \text{A}\beta \) neurotoxicity may also support this model. They did not refer to any relationship between \( \text{A}\beta \) aggregation and \( \text{A}\beta \)-induced \( \text{H}_2\text{O}_2 \) production. It may be that aggregated \( \text{A}\beta \) has more potent activity to induce \( \text{H}_2\text{O}_2 \) production than soluble \( \text{A}\beta \).

In addition to AD, there are numerous other human amyloidoses. Although those amyloids contain different proteins, all amyloidogenic peptides are characterized by the antiparallel \( \beta \)-sheet conformation (19). It was recently shown that these amyloidogenic peptides may share a common cytotoxic mechanism (20, 21). For example, three amyloidogenic peptides, i.e. amylin, calcitonin, and atrial natriuretic peptide, are all toxic to clonal and primary neurons and increase the intracellular \( \text{H}_2\text{O}_2 \) level (20). The cytotoxicity of these peptides is suggested to be mediated through a free radical pathway indistinguishable from that of \( \text{A}\beta \) (20). These observations imply that rifampicin could also inhibit the cytotoxicity of other amyloidogenic peptides.
peptides besides Aβ and that agents that inhibit amyloid fibril formation or cytotoxicity may have therapeutic potential for several different amyloidoses.

In summary, we have shown that rifampicin and its derivatives inhibit Aβ aggregation and neurotoxicity, and their inhibitory activities are attributed to the naphthohydroquinone or naphthoquinone structure, which possibly functions as a radical scavenger. Although the ansa chain appears not to be essential for the inhibitory activities, its lipophilicity may contribute to transport of the drug molecule into the brain in vivo (22). Our data presented here provide useful information for investigating the mechanisms of Aβ aggregation and neurotoxicity and developing new compounds for the treatment of AD.

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