Oral Administration of Histone Deacetylase Inhibitor MS-275 Ameliorates Neuroinflammation and Cerebral Amyloidosis and Improves Behavior in a Mouse Model

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Abstract

Alzheimer disease is the most common neurodegenerative disease and the major cause of dementia. In addition to β-amyloid aggregation and hyperphosphorylated tau, neuroinflammation also plays important roles in the pathophysiology of this multifactorial disorder. Histone deacetylase catalyzes deacetylation of histones and has important roles in the regulation of gene expression. Histone deacetylase inhibitors have been reported to exhibit neuroprotective and anti-neuroinflammatory activities and have therapeutic effects in several animal models of neurodegenerative diseases. Here, an efficient benzamide histone deacetylase inhibitor, MS-275, was orally administered by gavage to transgenic APP/PS1 mice, an animal model of cerebral amyloidosis for Alzheimer disease. After 10 days of treatment, MS-275 significantly ameliorated microglial activation and β-amyloid deposition in cerebral cortex and/or hippocampus. This was associated with improved nesting behavior, an important affiliative/social behavior. MS-275 also attenuated inflammatory activation of a mouse macrophage cell line in vitro. These results suggest that MS-275 may be a therapeutic option for Alzheimer disease and other neuroinflammatory diseases.

Key Words: Alzheimer disease, HDAC inhibitor, MS-275, APP/PS1 transgenic mouse, Cerebral amyloidosis, Neuroinflammation.

INTRODUCTION

Alzheimer disease (AD) is the most common neurodegenerative disease and the major cause of dementia. It is clinically defined by progressive cognitive and behavioral deficits and is characterized pathologically by extracellular deposits of aggregated β-amyloid (Aβ) peptide (senile/amyloid plaques) and intracellular deposits of hyperphosphorylated tau protein (neurofibrillary tangles).

Neuroinflammation plays important roles in the pathophysiology of this multifactorial disorder and, therefore, may represent an appropriate therapy for AD (1). Beta-amyloid peptides, the proteolytic products of amyloid precursor protein (APP) (2), are toxic and likely contribute to memory loss and neurodegeneration in AD (3). In CNS neuroinflammation, there is microglial activation, astrogliosis, and the release of numerous inflammatory mediators; glial activation is prominent around senile plaques (4, 5). Neuroinflammation may contribute independently to neural dysfunction and cell death, thereby establishing a self-perpetuating cycle by which inflammation induces further neurodegeneration (6). The understanding of neuroinflammation has led to the concept that anti-inflammatory agents may have beneficial effects for AD. In some prospective studies, anti-inflammatory treatments have delayed AD onset, ameliorated symptom severity, and improved or slowed cognitive decline (6).

Accumulating evidence suggests that dysregulation of epigenetic gene expression may play an important role during the onset of age-associated memory impairment and in the pathogenesis of neurodegeneration (7). Thus, epigenetic regulation may offer a new approach to understand and treat AD. Several studies have suggested that abnormal acetylation of histone is involved in the etiology and pathology of AD (8). Histone deacetylases (HDACs) may, therefore, be therapeutic targets for treatment of AD (9, 10). Histone deacetylase inhibitors can modulate the activities of HDAC, cause hyperacetylation of histones, and hence activate and/or repress gene subsets (11). Previous experimental treatments with pan-HDAC inhibitors, such as sodium butyrate, trichostatin A, suberoylanilide hydroxamic acid, or sodium phenylbutyrate, have shown promising therapeutic effects in rodent models of aging, brain injury, p25-mediated neuronal loss, and amyloid pathology (7, 12–15). These findings suggest that HDAC inhibitors are potential therapeutic agents for AD and other neurodegenerative diseases.

In addition to histones, nonhistone proteins, including certain transcription factors that play central roles in inflammation (e.g. nuclear factor-κB [NF-κB]) can be directly acetylated and thus also influenced by HDAC inhibitors (16). Recent studies indicate that HDAC inhibitors exhibit anti-inflammatory and neuroprotective effects in animal inflammatory disease models, such as experimental autoimmune encephalomyelitis, asthma, and allergic diseases (17). MS-275 is an efficient benzamide HDAC inhibitor specific for Class I HDACs, it preferentially inhibits HDAC1 versus HDAC3 (18, 19). In animal models of rheumatoid arthritis and neuritis, MS-275 effectively decreased immune cell infiltration and the local and/or serum level of inflammatory molecules (e.g. cytokines) and decreased tissue injury (20, 21). MS-275 exhibits immunomodulatory activities
A therapeutic effect of MS-275 in this mouse model, focusing on plasticity (25 responses, and impairment of cognitive function and synaptic pathology. Beta-amyloid plaque formation starts after 2 months in the neocortex and 4 months in the hippocampus. This is accompanied by dystrophic synaptic boutons, inflammatory responses, and impairment of cognitive function and synaptic plasticity (25–27). Our aim was to assess the potential therapeutic effect of MS-275 in this mouse model, focusing on Aβ deposition, neuroinflammation, and associated behavior.

**MATERIALS AND METHODS**

**Animals**

Breeding pairs of APP/PS1-21 mice with a C57BL/6J background were obtained from Prof. M. Jucker (University of Tübingen, Tübingen, Germany). Heterozygous male APP/PS1-21 mice were bred with wild-type C57BL/6J females (Charles River Germany, Sulzfeld, Germany). Offspring were tail-snipped and genotyped using polymerase chain reaction (PCR) with primers specific for the APP sequence (forward: ‘‘GAATTCCGACACTCTTCAGG’’; reverse: ‘‘GTTCTGCTGCATCTTGGACA’’). Mouse diets were provided by SSNIFF Spezialdiäten GmbH (Soest, Germany): diet number V1124-703 was for breeding pairs; diet number V2534-703 was for all the other mice. All experiments were licensed according to The German Animal Welfare Act (TierSchG) of 2006.

**Treatment With MS-275**

Three groups of animals were used. Group 1: 6 APP/PS1-21 mice (5 months old, 3 male and 3 female) were treated with MS-275 (Alexis Biochemicals, Loerrach, Germany). MS-275 (5 mg/kg body weight) suspended in 1% carboxymethylcellulose ([CMC] Blanose; Hercules-Aqualon, Düsseldorf, Germany) was fed daily by gavage for 10 days. Group 2: 6 control mice (sex- and age-matched APP/PS1-21 mice) received the same volume of 1% CMC dissolved in water. Group 3: 6 sex-matched APP/PS1-21 mice were untreated and were killed at the same age as mice in the other 2 groups.

**Design and Evaluation of Nest Construction Assay**

A nest construction assay was modified to determine the deficits in affiliative/social behavior of these APP/PS1 mice and potential changes after treatment (28). Mice were individually housed for at least 24 hours in clean plastic cages with approximately 1 cm of wood chip bedding lining the floor and identification cards coded to render the experimenter blind to sex, age, and genotype of mice. Mice were tested in counterbalanced groups of mixed genotypes and genders to reduce variability in housing conditions. At 2 hours before the onset of the dark phase of the light cycle, individual cages were supplied with a 20 × 20–cm piece of paper towel torn into approximately 5 × 5–cm square pieces.

The next morning (~16 hours later), cages were inspected for nest construction. Pictures were taken before evaluation for documentation. Paper towel nest construction was scored by a 3-point system: 1 = no biting or tears on the paper; 2 = moderate biting and/or tears on the paper but no coherent nest (i.e. not grouped into a corner of the cage); and 3 = the vast majority of paper torn into pieces and grouped into a corner of the cage (28).

MS-275–treated and control mice were killed after the 10-day treatment. Mice were deeply anesthetized with ether and perfused intracardially with 4°C 4% paraformaldehyde in PBS. Brains were quickly removed and postfixd in 4% paraformaldehyde overnight at 4°C.

**Immunohistochemistry and Image Evaluation**

Postfixed brains were cut into 2 hemispheres; hemispheres were embedded in paraffin, serially sectioned (3 μm) and mounted on silan-covered slides. Hemispheres sections were stained by hematoxylin and eosin or immunohistochemistry, as described previously (29). The following antibodies were used: anti–β-amyloid (1:100; ab2539, Abcam, Cambridge, UK) for Aβ deposition, Iba-1 (1:200; Wako, Neuss, Germany) for activated microglia, and glial fibrillary acidic protein ([GFAP] 1:500; Chemicon [Millipore], Billericia, MA) for astrocytes. The rabbit polyclonal anti–β-amyloid antibody (ab2539) was generated against the synthetic peptide DAERFHDSGYEVHH conjugated to KLH, corresponding to amino acids 1–14 of human β-amyloid. Based on regular immunolabeling of Aβ (brown), several sections were further double stained for GFAP (blue), which was developed with Fast Blue BB salt chromogen-substrate solution.

Stained hemisphere sections were examined by light microscopy (Nikon Coolscope; Nikon, Düsseldorf, Germany), but only 1 hemisphere section from each animal was used in quantification and further analysis, that is, 6 sections per group.

Beta-amyloid deposition and Iba-1 and GFAP immunostaining were evaluated at cross sections of hemispheres; evaluations focused on neocortex and hippocampus. All sections were randomly numbered and analyzed independently by 2 observers who were not aware of the treatment and time points. Beta-amyloid plaques and Iba-1–positive and GFAP-positive cells in neocortex and hippocampus were manually counted.

To evaluate immunostaining data further, area percentages of specific immunoreactivity (IR) in selected regions were calculated. Briefly, images of hemisphere cross sections were captured under 5× magnification using Nikon Coolscope with fixed parameters; the neocortex and hippocampus areas were manually outlined on these photos and further analyzed using the software MetaMorph Offline 7.1 (Molecular Devices, Toronto, CA). Areas of IR were selected by color threshold segmentation, and all parameters were fixed for all images. Results were given as group medians of plaque/cell counts or area percentages of IR to interest areas on cross sections and quartiles.
In Vitro Cell Culture

The immortalized murine macrophage cell line RAW 264.7 was used to determine effects of MS-275 on macrophage phenotype in vitro. RAW 264.7 cells were grown in complete RPMI 1640 media (Gibco, Grand Island, NY) containing penicillin (100 U/mL), streptomycin (100 U/mL), and 10% fetal calf serum at 37°C and 5% carbon dioxide. Cells (10⁵) were seeded into 12-well cell culture plates and cultured for 24 hours. Afterward, cells were stimulated with lipopolysaccharide ([LPS] working concentration of 5 μg/mL; stock solution 1 mg/mL in PBS) for 12 hours. MS-275 (working concentration of 20 ng/mL, 84 nmol/L; stock solution 10 mg/mL, 42 mmol/L in DMSO) was then added, and cells were incubated for another 24 hours. Thereafter, cells were harvested and centrifuged, and supernatants were collected for analysis of nitric oxide (NO) concentration by standard Griess assay (Sigma, Munich, Germany). Total RNA from cultured cells was prepared using the RNeasy Mini Kit (Qiagen GmbH, Hilden, Germany) according to the manufacturer’s instruction. One microgram RNA was reverse transcribed into cDNA using QuantiTect Reverse Transcription Kit (Qiagen). Messenger RNA expression levels for interleukin-1β (IL-1β), inducible NO synthase (iNOS), and tumor necrosis factor (TNF) were measured by real-time PCR. In addition, cell viability of treated RAW cells was detected by MTT colorimetric assay.

Statistical Analysis

Difference of plaque/cell counts, area percentages, nesting scores, and results from in vitro study between MS-275 treatment and controls were analyzed by exact nonparametric Mann-Whitney U test (Graph Pad Prism 5.0 software). For all statistical analyses, significance levels were set at p < 0.05. Plaque/cell counts or area percentages of the 5-month group are shown to demonstrate that vehicle treatment did not affect the transgenic mice compared with vehicle-treated littermates. Results are presented as group medians (quartiles) with points for each case.

RESULTS

Effect of MS-275 on Behavioral Impairment

Before the start of treatment, impaired nest construction was observed in the APP/PS1 (1.5 [1.2, 1.9]) versus naive control (3.0 [2.6, 3.0]) mice (p < 0.05; n = 6) (Fig. 1). Right at the beginning of treatment (Day 1), there were no significant differences in nest construction between the MS-275 group and the control group. After 10 days of treatment (Day 11), there was a significant difference between MS-275 and control-treated groups. (D, E) Examples of nests after supplied paper towel material from control (D) and MS-275 (E)-treated groups. * p < 0.05.
treatment mice (MS-275 group, 2.1 [1.7, 2.4]; control group, 1.8 [1.5, 2.4]; \( p > 0.05; n = 6 \), Fig. 1). After 10 days of treatment, relatively immediate chewing and tearing of the paper towels by the MS-275–treated mice were observed, and pieces were grouped into a corner of the cage. In contrast, the control APP/PS1 mice slightly chewed but did not destroy the paper towels.

**FIGURE 2.** Oral MS-275 treatment reduced \( \beta \)-amyloid deposition and microglial activation in APP/PS1 mice. The brains of MS-275– and vehicle-treated mice and another control group of 5-month-old untreated age- and sex-matched littermates were analyzed using immunohistochemistry. Results are shown as group medians (quartiles) with points for each case. (A) In the cortex of APP/PS1 mouse brains from the MS-275 group, there were fewer \( \beta \)-amyloid plaques. (B) Immunoreactivity area percentages of \( \beta \)-amyloid staining were reduced by nearly 50% in the cortex after MS-275 treatment. (C) In the hippocampus (hippo), there was no significant reduction of plaque counts. (D) In the hippocampus, the IR area of \( \beta \)-amyloid deposition was significantly decreased by MS-275. (E) In the cortex, Iba-1 IR was reduced by nearly one half in the MS-275 treatment group. (F) There was slightly decreased Iba-1 IR in the hippocampus. There were no significant differences in either cortex or hippocampus between the vehicle-treated and untreated mice in terms of plaque counts and IR areas. The Mann-Whitney U test was performed to compare differences between control and MS-275 treatment. * \( p < 0.05 \).

**FIGURE 3.** Effects of MS-275 on \( \beta \)-amyloid deposition and microglial activation in the brains of APPP/PS1 mice. (A–H) Representative images show \( \beta \)-amyloid (A, C, E, G) and microglial activation (B, D, F, H) after MS-275 treatment. There are larger and more numerous \( \beta \)-amyloid plaques in the cortex of control mice (A) than in the MS-275 group (C). Anti-Iba-1 staining on serial sections shows more numerous immunopositive microglia and larger IR areas in the control cortex (B) than in the treated mouse cortex (D). Most Iba-1–positive microglia accumulate around \( \beta \)-amyloid plaques. In the hippocampus of a control mouse (E), there are more numerous and slightly larger \( \beta \)-amyloid deposits than in the MS-275–treated mouse hippocampus (G). (F, H) Iba-1 staining on adjacent serial sections shows that most Iba-1–positive microglia are clustered around \( \beta \)-amyloid plaques, but there are also numerous Iba-1–positive cells distributed throughout the hippocampus. There is no obvious decrease of Iba-1 IR in the MS-275–treated hippocampus (H).
Effect of MS-275 on Aβ Deposition

Amyloid plaques were distributed throughout the whole cortex of 5-month-old APP/PS1 transgenic mice; some of these are small dense core plaques, and others are larger plaques with a dense core and a large halo of diffuse amyloid. Lower plaque densities were seen in the hippocampus, which is in accordance with the original report that amyloid plaques appeared first in the cortex at 6 weeks of age and later in the hippocampus of APP/PS1-21 transgenic mice (26). No significant differences in Aβ deposition in cortex and hippocampus were observed between control-treated APP/PS1 mice and their untreated age- and sex-matched littermates (Fig. 2A–D). In the cortex of APP/PS1 mouse brains from the MS-275 group, there were significantly fewer amyloid plaques counted versus the control group (MS-275, 98.0 [86.5, 123.3]; control, 150.0 [111.8, 166.5]; p < 0.05; n = 6) (Fig. 2A).

In the hippocampus, however, there was no significant reduction in plaque counts (MS-275, 9.0 [7.3, 12.3]; control, 11.5 [7.8, 16.3]; p > 0.05; n = 6, Fig. 2C).

Area percentages of Aβ deposition (IR positive pixels) were reduced by nearly 50% in cortex (MS-275, 0.23% [0.20, 0.30]; control, 0.40% [0.32, 0.61]; p < 0.05; n = 6) (Fig. 2B). Area percentages of Aβ deposition were also decreased significantly in the hippocampus (MS-275, 0.14% [0.08, 0.15]; control, 0.17% [0.14, 0.19]; p < 0.05; n = 6) (Fig. 2D). Smaller plaques and fewer branches were observed in brains from the MS-275 than the control group (Fig. 3A, B; 4A, B).

Therefore, reduction was more apparent in measurements of Aβ IR areas than plaque counts (Fig. 2).

Effect of MS-275 on Microglial and Astrocyte Activation

In both cortex and hippocampus, amoeboid Iba-1–positive microglia, characterized by the fine tortuous branching, were observed clustered around amyloid deposits, (Fig. 3B, D, F, H). As for Aβ deposition, no significant difference of Iba-1 IR area (Iba-1 positive pixels) in cortex and hippocampus was observed between control-treated and untreated APP/PS1 mice (Fig. 2E, F). Iba-1–positive cell counts in cortex of MS-275–treated and control-treated mice were not significantly different, but analysis of immunostaining with software MetaMorph showed that Iba-1 IR area was reduced by nearly one half in cortex of MS-275–treated versus controls; there was a significant difference in scores between the MS-275 and control groups after the treatment, that is, on Day 11 (MS-275 group, 2.4 [2.3, 3.0]; control group, 1.5 [1.2, 2.4]; p < 0.05; n = 6; Fig. 1). Examples of nests after paper towel material was supplied to the MS-275 and control groups after the treatment, that is, on Day 11 (MS-275 significant difference in scores between the MS-275 and control groups; Figs. 1D, E).

FIGURE 4. Effects of MS-275 on plaques, microglia morphology, and GFAP expression. (A, B) Representative images show typical Aβ-immunopositive plaques in cerebral cortex of control (A) and MS275-treated (B) mice. (C, D) There are more clustered amoeboid Iba-1–positive microglia in the control mouse brain (C), characterized by more fine tortuous branching, compared with those in the MS-275–treated mouse (D). (E, F) Double immunostaining shows that GFAP expression is widely distributed throughout the hippocampus (E) and cortex (F), exhibiting no obvious plaque-related distribution pattern, especially in the hippocampus (Aβ, brown; GFAP, blue). They all show typical morphology of astrocytes, including stellate shape and multiple branched processes. No differences in treated and control brains with respect to GFAP immunostaining were identified.

towels, that is, their behavior did not change. There was a significant difference in scores between the MS-275 and control groups after the treatment, that is, on Day 11 (MS-275 group, 2.4 [2.3, 3.0]; control group, 1.5 [1.2, 2.4]; p < 0.05; n = 6, Fig. 1). Examples of nests after paper towel material was supplied to the MS-275–treated and control groups are shown (Fig. 1D, E).

FIGURE 5. MS-275 attenuates inflammatory activation of macrophage RAW 264.7 cells in vitro. Cells were stimulated with LPS (5 μg/mL) for 12 hours; MS-275 (20 ng/mL, 84 nmol/L) was then added, and the cells were incubated for another 24 hours. (A) Supernatants were collected for the analysis of NO concentrations by a standard Griess assay. * p < 0.05 compared with LPS alone group. (B) Total RNA from cultured cells was prepared, and mRNA levels of IL-1β, iNOS, and TNF were measured by real-time PCR. The exact nonparametric Mann-Whitney U test was performed to compare differences between PBS control and MS-275 treatment. * p < 0.05, ** p < 0.01 versus the respective LPS-alone group.
only a slight decrease in hippocampus. In cortex of MS-275–treated mice, most Iba-1–positive cells were less clustered and showed morphology with less branching, indicating reduced microglial activation compared with those in controls (Fig. 4C, D).

Numerous GFAP-positive cells were widely distributed throughout the hippocampus and cortex, exhibiting, however, no obvious plaque-related distribution pattern (Fig. 4E, F). They all showed typical morphology of astrocytes, including stellate shape and multiple branched processes; some of them had the typical morphology of perivascular astrocytes. No significant changes in GFAP-positive cell intensity were observed between MS-275 treatment and controls; GFAP IR areas were only slightly decreased after MS-275 treatment (data not shown).

**MS-275 Attenuated Inflammatory Activation of Macrophages In Vitro**

After LPS induction, NO production and mRNA expression of TNF, IL-1β, and iNOS were significantly increased, indicating inflammatory activation of RAW cells (Fig. 5A, B). MS-275 treatment significantly reduced NO concentration in the media and attenuated mRNA expression of TNF, IL-1β, and iNOS (Fig. 5A, B), suggesting effective anti-inflammatory activity. Part of these data and further results of this in vitro study have been published (23). Very low expression levels of inflammatory molecules were detected in the control group without LPS stimulation (data not shown). Additional MTT assay showed no significant difference in cell viability between the different groups (23).

**DISCUSSION**

In this work, we describe several beneficial effects of oral treatment with MS-275, an efficient HDAC-1 inhibitor, in a transgenic rodent model of cerebral amyloidosis. MS-275 treatment effectively attenuated microglial activation in the cortex and reduced Aβ deposition in cortex and hippocampus of APP/PS1 mice. This was associated with improved nesting behavior, an important type of affiliative/social behavior that is impaired in APP-overexpressing mice.

Deacetylation of histones, which is catalyzed by HDAC and modulated by HDAC inhibitors, plays important roles in the regulation of gene expression (30). During the last decade, studies have focused on HDACs as targets for the treatment of human neurodegenerative diseases because increasing in vitro and other data suggest HDAC inhibitors as a potential therapeutic option (31). Several HDAC inhibitors have been reported to have therapeutic effects in animal models of different neurodegenerative diseases, such as inhibitors targeting HDAC3 and HDAC1 in model systems of Huntington disease (32) and the pan-HDAC inhibitor valproic acid (VPA) in a mouse model of Parkinson disease (33). Furthermore, in animal models of AD, trichostatin A, 4-phenylbutyrate, sodium butyrate and several inhibitors of HDAC class I attenuated neuropathology or improved cognitive/behavioral deficits. In particular, a previous in vitro and in vivo study reported that VPA inhibited Aβ production by altering APP processing, thus attenuating plaque formation and behavioral deficits in a similar rodent model of cerebral amyloidosis (37). Valproic acid was also reported to downregulate the expression of APP in vitro (38). Compared with many other HDAC inhibitors, especially to VPA, MS-275 is a more potent, long-lasting, brain region-selective inhibitor of HDAC (39).

An important role for neuroinflammation has been reported in both rodent models and human AD (6), and attenuated neuroinflammation contributes to reduced phosphorylated tau protein and Aβ plaque accumulation (40). The general anti-inflammatory property of HDAC inhibitors has been characterized (41), and recently, their anti-neuroinflammatory and neuroprotective effects have also been reported in various animal models (29, 42, 43). Nonhistone proteins, such as the transcription factor NF-κB, which controls many genes involved in inflammation, can also be directly acetylated and modulated by HDAC inhibitors (44), which may contribute to a more direct and faster anti-inflammatory effect. We previously showed that MS-275 treatment attenuated reduced cellular infiltration and inflammatory molecules in experimental autoimmune neuritis (21). Previous studies indicate that therapeutic strategies controlling the activation of microglia and the excessive production of proinflammatory and pro-oxidant factors may be effective in controlling neurodegeneration in dementia (45). Nitric oxide has been linked to neurodegenerative disorders because of the increased expression of several neurodegeneration-relevant enzymes. Nitrated proteins have also been detected in neurodegenerative diseased tissues, revealing that NO is biologically active in regions undergoing neurodegeneration (46). The main proinflammatory cytokines, for example, TNF, IL-1β, and IL-6 produced by microglia, have been shown to be involved in the development of neuroinflammation and were reported to correlate with amyloid load in a similar transgenic mouse model (47). Our in vitro study showed that MS-275 effectively attenuated the production of NO and proinflammatory cytokines/molecules in a macrophage cell line. MS-275 attenuated the microglial activation in cortex of APP/PS1 transgenic mice, suggesting an inhibitory effect of MS-275 on neuroinflammation in this animal model, which might have contributed to the ameliorated pathology and improved behavioral scores.

There were no obvious or significant changes in GFAP expression and astrogliosis after treatment. This may be explained by relatively early age of these APP/PS1 mice and the short-term treatment. In particular, the distribution pattern of GFAP expression did not seem to be plaque associated, particularly in the hippocampus, suggesting that astrocyte activation/GFAP expression may not be associated with Aβ deposition at this relatively early age of APP/PS1 mice.

Previous studies reported a correlation of reduced histone acetylation with cognitive decline or behavioral deficits in animal models of neurodegeneration, including models of AD. Accordingly, experimental treatments by HDAC inhibitors have shown promising results in reversing cognitive deficits and improving behaviors in some of these distinct AD models (48). MS-275 increased histone acetylation specifically in the brain areas associated with behavioral and cognitive deficits of mice (39). However, cognitive/memory deficits can only be observed after the age of 8 months in the APP/PS1 model (26). Not only cognitive impairment but also disturbances in nonmnemonic/cognitive behaviors are found in most AD mouse models and are considered very valuable...
for modeling human AD; these models are thus routinely used to evaluate potential therapeutic interventions targeting toxic species of Aβ protein (49). Nesting behavior is an affiliative social behavior and is important for the survival of animals. Impaired nesting behavior of both male and female mice has been observed in the AD rodent model Tg2576, overexpressing APP, even at the very young age of 2 months (28). Beta-amyloid deposition and APP-related toxic factors are believed to lead to abolished nesting behavior (28). We similarly observed impaired nesting behavior that was improved after the 10-day MS-275 treatment. Considering the relatively short-term treatment, reduced neuroinflammation, Aβ deposition, and APP-related toxic factors may contribute to the improved affiliative/social behavior.

Taken together, MS-275 oral treatment effectively ameliorated neuroinflammatory reaction and cerebral amyloidosis and restored impaired affiliative/social behavior in a rodent cerebral amyloidosis model, suggesting that MS-275, or potentially other HDACs, may be promising therapeutic options for AD or neurodegenerative diseases.

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REFERENCES


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