Linalool reverses neuropathological and behavioral impairments in old triple transgenic Alzheimer’s mice

Angélica María Sabogal Guáqueta*, Edison Osoriob, Gloria Patricia Cardona-Gómez**

*Neuroscience Group of Antioquia, Cellular and Molecular Neurobiology Area - School of Medicine, SIU, University of Antioquia UdeA, Calle 70 No, 52-21, Medellín, Colombia

**Grupo de Investigación en Sustancias Bioactivas, Facultad de Ciencias Farmacéuticas y Alimentarias, Universidad de Antioquia UdeA, Calle 70 No, 52-21, Medellín, Colombia

Chapter 2

1. Introduction

Alzheimer’s disease (AD), a progressive neurodegenerative disorder, is the most common form of dementia. AD is responsible for a considerable human, social and economic burden around the world (Association, 2014). In Latin America, the main causes of dementia are a sedentary lifestyle, metabolic disorder, and cardiovascular and cerebrovascular diseases (Kalaria et al., 2008). In general, AD patients present with a gradual deterioration of episodic memory, a global decline in cognitive function, and behavioral changes. AD symptoms are the clinical manifestations of a progressive accumulation of intra- and extracellular β-amyloid, the formation of neurofibrillary tangles (NFTs) and the extensive oxidative stress associated with neuron and synapse loss (Ittner and Gotz, 2011; Reitz and Mayeux, 2014).

The current standard pharmacotherapy for cognitive improvement in AD patients includes acetylcholinesterase inhibitors, such as galantamine, and the N-methyl-D-aspartate (NMDA) antagonist memantine, which promote cognitive function in patients with moderate to severe AD (Kang et al., 2014). However, the approval of these drugs has not been based on their ability to slow disease progression but on their ability to improve clinical symptomatology. Hence, only symptomatic drugs with transient benefits have been approved for clinical use in AD patients by the US Food and Drug Administration (FDA) (Bassil and Grossberg, 2009). The use of alternative therapies for neuroprotection is increasing; these alternatives include natural products, such as monoterpenes (Dinda et al., 2009; Tabassum et al., 2015).

(−)-Linalool, one enantiomer of the naturally occurring monoterpene, is a major volatile component of essential oils in several aromatic plant species, such as Lavandula angustifolia Mill., Melissa officinalis L., Rosmarinus officinalis L. and Cymbopogon citratus DC. Interestingly, many linalool-producing species are traditionally used in folk medicine and in aromatherapy to relieve symptoms and to cure a variety of acute and chronic ailments (Batista et al., 2010; Elisabetsky et al., 1995). Linalool is widely used in the manufacture of fragrances for shampoos, soaps and detergents and in pharmaceutical drug formulations (Letizia et al., 2003; Mitic Culafic et al., 2009).

Linalool exhibits a variety of pharmacological effects, including antimicrobial, antileishmanial, anti-inflammatory, anti-oxidant and cardiovascular effects, in normotensive and hypertensive rats (Anjos et al., 2013; Beier et al., 2014; Celik and Ozkaya, 2002; Huo et al., 2013; Wu et al., 2014). The strong antioxidant activity of linalool inhibits LDL oxidation; this inhibition enhances cholesterol uptake via macrophage scavenger receptors. Linalool significantly reduced plasma TG, total cholesterol and HMG-CoA levels, demonstrating in vivo anti-atherogenic activity (Cho et al., 2011; Chung et al., 2008). Linalool has remarkable effects on the central nervous system (CNS), acting as a sedative, antinociceptive, anticonvulsant and anxiolytic (Batista et al., 2010; de Almeida et al., 2009; Elisabetsky et al., 1999; Linck...

Abstract

Alzheimer’s disease (AD) is an age-related progressive neurodegenerative disorder. Several types of treatments have been tested to block or delay the onset of the disease, but none have been completely successful. Diet, lifestyle and natural products are currently the main scientific focuses. Here, we evaluate the effects of oral administration of the monoterpene linalool (25 mg/kg), every 48 h for 3 months, on aged (21e24 months old) mice with a triple transgenic model of AD (3xTg-AD) mice. Linalool-treated 3xTg-AD mice showed improved learning and spatial memory and greater risk assessment behavior during the elevated plus maze. Hippocampi and amygdalae from linalool-treated 3xTg-AD mice exhibited a significant reduction in extracellular β-amyloidosis, tauopathy, astrogliosis and microgliosis as well as a significant reduction in the levels of the pro-inflammatory markers p38 MAPK, NOS2, COX2 and IL-1β. Together, our findings suggest that linalool reverses the histopathological hallmarks of AD and restores cognitive and emotional functions via an anti-inflammatory effect. Thus, linalool may be an AD prevention candidate for preclinical studies.

Keywords: Alzheimer’s disease, linalool, behavior function, inflammation
et al., 2009). Linalool also modulates glutamatergic neurotransmission both in vitro and in vivo, possibly through NMDA receptor interactions (Elisabetsky et al., 1995; Silva Brum et al., 2001). However, nothing is known about linalool’s effect on AD neuropathology and behavioral impairments, which is the goal of the present study.

2. Materials and methods

2.1. Animals
Homozgyous triple transgenic AD model (3xTg-AD) and non-transgenic (Non-Tg) mice (Oddo et al., 2003) from the in-house colony at the University of Antioquia maintained in the SIU (Sede de Investigacion Universitaria) specific pathogen-free vivarium in Medellin, Colombia were used at ages from 18 to 21 months to obtain a homogenous penetrance of tauopathy. The mice were maintained on a 12:12 h dark: light cycle and received food and water ad libitum. The animals were handled according to Colombian standards (law 84/1989 and resolution 8430/1993) and guidelines. Special care was taken to minimize animal suffering and to reduce the number of animals used.

2.2. Administration of drugs
Linalool (Sigma Aldrich, Cat: L2602) was dissolved in phosphate-buffered saline (PBS). The 3xTg-AD mice received 25 mg/kg linalool or saline solution (vehicle) orally every 48 h for 3 consecutive months beginning at 18-21 months of age and were sacrificed at ages of 21-24 months (Fig. 1). The linalool dose (25 mg/kg) is not toxic (Brickers et al., 2003; Api et al., 2015), and the interval between the final drug treatment and the assays were selected based on previous in vivo studies (Huo et al., 2013; Mehri et al., 2014; Nascimento et al., 2014). We carefully monitored the general health of the mice throughout the linalool treatment and did not observe any adverse effects.

2.3. Histology
Twenty-four hours after the final behavioral test, the animals were anesthetized intraperitoneally using a mixture of ketamine (50 mg/kg) plus xylazine (20 mg/kg) and were perfused with normal saline and 4% paraformaldehyde (0.1 M PBS, pH 7.4). Brains were removed and post-fixed with 4% paraformaldehyde at 4 °C for 48 h and then cryopreserved with 30% sucrose and stored at -20 °C. The brains were sectioned (50 μm) with a Leica VT1000S vibrating blade microtome (Leica Microsystems, Germany).

2.4. Immunohistochemistry
The coronal sections (50 μm) were permeabilized and blocked with 0.3% Triton X-100 and 1% BSA in PBS and were then probed with primary antibodies: anti-beta amyloid antibody (beta amyloid 1-16 (6E10) Monoclonal #SIG-39320, Covance, 1:500), antiphospho-PHF-tau (pSer202/Thr205 Antibody (AT8) MN1020, Thermo Scientific, 1:500), anti-GFAP (tau (pSer202/Thr205 Antibody (AT8) #MN1020, Thermo Scientific, 1:500), anti-GFAP, anti-Phospho-PHF-1% BSA in PBS and were then probed with primary antibodies: anti-beta amyloid antibody (beta amyloid 1-16 (6E10) Monoclonal #SIG-39320, Covance, 1:500), antiphospho-PHF-2.4. Immunohistochemistry and subiculum (hippocampus), entorhinal cortex (EC) and amygdala were evaluated at 10x or 40x magnification and analyzed using ImageJ 1.45 software. Staining Kit, Pierce #32020, 1:250 reagent A:B) for 1h. Once the complex was removed, diaminobenzidine (DAB) was used as developer. The sections were dehydrated with alcohol, cleared with xylene and sealed with Consul-mount. The immunoreactivity in the tested areas was quantified at 10x or 40x magnification and analyzed using ImageJ 1.45 software (NIH, USA). The absence of primary antibody did not result in immunoreactivity. The CA1 and subiculum (hippocampus), entorhinal cortex (EC) and amygdala were evaluated at bregma 1.76 mm posterior to bregma (Paxinos and Franklin, 2004).

2.5. Immunofluorescence
Sections at the level of the bregma were rinsed in 0.1 M PBS and incubated for 10 min with 50 mM ammonium chloride to prevent autofluorescence. The sections were preincubated for 60 min at room temperature with Triton X-100 in PBS (TXPBS) and 3% BSA and then incubated overnight at 4°C with the following primary antibodies: anti-beta amyloid antibody (beta amyloid 1-16 (6E10) Monoclonal #SIG-39320, Covance, 1:500) and anti-Iba1 (Rabbit Anti-Iba1 (Ionized calcium binding adaptor molecule) #019e19741, Wako, 1:500) and the appropriate secondary antibodies (1:250 concentration, goat anti-rabbit IgG (H+L) biotin conjugated, Pierce #31822 or goat Anti-Mouse IgG (H+L) Biotin Conjugated Pierce #31800). Later, tissues were incubated with avidin biotin complex (ABC Standard Peroxidase Staining Kit, Pierce #32020, 1:250 reagent A:B) for 1h. Once the complex was removed, diaminobenzidine (DAB) was used as developer. The sections were dehydrated with alcohol, cleared with xylene and sealed with Consul-mount. The immunoreactivity in the tested areas was quantified at 10x or 40x magnification and analyzed using ImageJ 1.45 software (NIH, USA). The absence of primary antibody did not result in immunoreactivity. The CA1 and subiculum (hippocampus), entorhinal cortex (EC) and amygdala were evaluated at bregma 1.76 mm posterior to bregma (Paxinos and Franklin, 2004).

2.6. Behavioral test
At 21-24 months of age, the animals were administered orally by gavage to 18-21-month-old Non-Tg and 3xTg-AD mice for 3 months, every 48 h. Learning and memory were evaluated in the Morris water maze test (five days, ten trials) at 21-24 months of age. Afterward, the elevated plus maze was performed over two days. Then, the mice were sacrificed for histological and biochemical analyses.

2.7. Statistical analysis
All values are expressed as mean ± standard error of the mean (SEM). Data were analyzed using the two-tailed Student’s t-test. Differences were considered statistically significant at *p < 0.05.*
2.6. Morris water maze test

Forty-eight hours after the final treatment, the animals were evaluated in the Morris water maze (MWM). A white plastic tank 1 m in diameter and 30 cm in height was filled with water (22 ± 2°C) to a depth of 20 cm. The platform (7 cm diameter) was 1.5 cm below the surface of the water during spatial learning and 1.5 cm above the surface of the water during the visible session. Extra-maze visual cues around the room remained in a fixed position throughout the experiment. Ten sessions or trials were performed, two complete sessions per day over five days. Each session consisted of four successive subtrials (30 s inter-trial interval), and each subtrial began with the mouse placed pseudo-randomly in one of four starting locations. The animals had been trained to stay on the platform for 30 s prior to the initial trial. The latency to reach the platform was evaluated using a visible platform to control for any difference in visual-motor abilities or motivation between the experimental groups. If a mouse did not locate the platform after a maximum of 60 s, it was gently guided to the platform. Then, the animals were then provided with 48 h of retention time, followed by a probe trial of spatial reference memory, in which the animals were placed in the tank without the platform for 60 s (Fig. 1). The latency to reach the exact former platform location and the number of crossings of the platform target quadrant were recorded during the probe trial. An automated system (Viewpoint, Lyon, France) recorded the behavior of the animals” (Sabogal-Guaqueta et al., 2015).

2.7. Elevated plus maze

Twenty-four hours after the visible test in the Morris water maze, the animals were exposed to the elevated plus maze (EPM). The apparatus was made of white Plexiglas and illuminated using approximately 30-40 lux. The EPM consisted of two open arms (30x 5x 0.25 cm) and two closed arms (30x 5x 15 cm) extending from a common central platform (5x 5 cm), and the entire apparatus was elevated by a single central support to a height of 60 cm above floor level. Each mouse was placed in the middle section facing an open arm and left to explore the maze for a single 5 min session with the experimenter out of view. After each trial, the floor was wiped clean with 10% alcohol.

The frequency of open entries (arm entry defined as all four paws into an arm) and the amount of time spent by the animals in open sections of the maze were recorded. We also calculated the % open entries (open entries/total entries x 100) and the % time spent in open arms (open time/300 x 100). We also recorded the rearing frequency and duration (all rearing occurred against the walls of the enclosed arms), the frequency of discrete behaviors, such as head dipping (exploratory movement of head/shoulders over sides of the maze), and the duration of grooming (species-typical sequence beginning with the snout, progressing to the ears, and ending with whole-body grooming). Each experiment was videotaped using a high-resolution video camera. These data were collected using X-Plo-Rat 2005 software (Taverna-Chaim and Morato, 2008).

2.8. Western blotting

After behavior testing, the animals were sacrificed by decapitation, and the hippocampus and amygdala were dissected and immediately frozen in liquid nitrogen and stored at 80°C until analysis. The tissues were dissected and homogenized in lysis buffer according to a described previously protocol (Cardona- Gomez et al., 2004). Membranes were incubated overnight with the following primary antibodies: PHF-1 monoclonal antibody, which recognizes Tau pSer-396/404 and was donated by P. Davies (Feinstein Institute for Medical Research, Manhasset, NY); antiphospho-PHF-tau (pSer202/Thr205 Antibody (AT8) #MN1020, Thermo Scientific, 1:500); anti-NOS2 (C-11) Ms mAb (# Sc 7271, Santa Cruz Biotechnology, 1:100); rabbit polyclonal anti-COX2 (#AB15191, Abcam, 1:1000); rabbit phospho-p38 MAPK Thr180/ Tyr182 (# 9215, Cell Signaling, 1:1000); and tubulin (Mouse monoclonal anti-BIII tubulin antibody, #G712A, Promega, 1:10000) as a loading control. IRDye 800CW goat anti-rabbit (LI-COR; diluted 1:10000) was used as a secondary probe. The blots were visualized using an Odyssey Infrared Imaging System (LI-COR Biosciences, United States).

2.9. β-Amyloid and IL-1β ELISA

Brain levels of soluble Aβ 1-40 and 1-42 were measured using ELISA. Soluble Aβ levels were measured by sandwich capture ELISA using Colorimetric BetaMark -βAmyloid x-40 (SIG-38954- Covance Laboratories) and x-42 ELISA (SIG-38956- Covance Laboratories) kits. IL-1β was measured using a Quantikine ELISA Mouse IL-1β (Cat. #MLB00C, R&D Systems, Minneapolis, USA) kit following the manufacturer’s protocol at a protein concentration of 50 μg/mL.

2.10. Statistics

At least 3 mice were used for each histological study; 4-6 mice were used for each biochemical study; and 4-5 mice and 10-12 mice were used for EPM and MWM, respectively. Parametric data were evaluated with analysis of variance (ANOVA) to compare the 4 groups and then with Tukey’s test for post hoc multiple comparison between-group analyses. Nonparametric data were evaluated using the Kruskal-Wallis test. The escape latency during the training and the transfer test was tested using two-way ANOVA followed by a Dunnett’s post hoc test for multiple comparisons. The statistical analysis was performed using GraphPad Prism software (version 6.0), and the results were considered significant when p ≤ 0.05. The values are expressed as the means ± SEM.

3. Results

3.1. Linalool treatment reversed spatial memory impairment in old 3xTg-AD mice

The MWM test is one of the most widely accepted behavioral tests for monitoring spatial learning and memory skills, which primarily depend on the hippocampus. Non-Tg mice...
Linalool reverses neuropathological and behavioral impairments in old triple transgenic Alzheimer’s mice

Chapter 2

Linalool reverses neuropathological and behavioral impairments in old triple transgenic Alzheimer’s mice

3.2. Anxiolytic activity after oral administration of linalool in aged 3xTg-AD mice

We analyzed the effect of linalool on anxiety using the EPM test (Campos et al., 2013). Our data show a significant increase in the percentage of open-arm entries and the time spent in the open arms when comparing the 3xTg-AD mice treated with linalool to the Non-Tg and 3xTg-AD vehicle-treated mice, which rarely visited the open arms (Fig. 3 a-b). Additionally, 3xTg-AD vehicle mice showed a trend towards an increased number of grooming events and a significantly long amount of time spent grooming compared to those of the Non-Tg mice and the 3xTg-AD linalool-treated mice (Fig. 3 c-d). The number of occurrences of and time spent head-dipping were reduced in 3xTg-AD mice; in 3xTg-AD linalool treated mice, these values were restored to levels similar to those of the Non-Tg control mice (Fig. 3 e-f). This head-dipping behavior was inversely proportional to the number of rearing and the time spent rearing, which predominantly occurred in the closed arms. Therefore, rearing was significantly lower in the linalool-treated 3xTg-AD mice than in the other experimental groups (Fig. 3 g-h).

3.3. Aged 3xTg-AD linalool-treated mice show reduced β amyloidosis

3xTg-AD vehicle-treated mice showed the typical amyloid deposition found in the Non-Tg mice (Oddo et al., 2003), and this deposition was significantly reduced in the hippocampus, entorhinal cortex and amygdala of the 3xTg-AD linalool-treated mice (Fig. 4 a-e). The linalool treatment did not completely eliminate β-amyloidosis in the 3xTg-AD mice. The decrease in β-amyloid levels was accompanied by a significant reduction in β-amyloid 1-40 and 1-42 protein levels in the hippocampal lysates of the linalool-treated 3xTg-AD mice compared to the vehicle-treated 3xTg-AD mice (Fig. 4 f-g). Together, these data show that cerebral amyloidosis, including amyloid deposits and β-amyloid peptide abundance, was delayed by the oral administration of linalool in old 3xTg-AD mice.

3.4. Linalool treatment ameliorated tau hyperphosphorylation in aged 3xTg-AD mice

Several abnormal tau hyperphosphorylation sites in AD have been identified using the increased tau aggregation at 18 months in the 3xTg-AD model (Oddo et al., 2003) We explored the effect of linalool on tau pathology in the brains of old 3xTg-AD mice using AT-8 immunoreactivity. 3xTg-AD mice treated with linalool displayed a significant decrease in pair helical filaments (PHFs) in the CA1 area, the subiculum and the amygdala but not in the EC. These findings were similar to the AT-8 immunoreactivity observed in the Non-Tg vehicle-treated mice (Fig. 5 e). We also found a significant reduction in PHF-1 protein levels in the hippocampal lysates from linalool-treated 3xTg-AD mice compared with vehicle-treated mice, suggesting a reduction in NFTs (Fig. 5 f).

3.5. Linalool decreased the inflammatory response in old 3xTg-AD mice

Chronic activation of glial cells around amyloid plaques is associated with AD pathophysiology via the production of numerous neurotoxic reactants, proinflammatory...
cortisol, and immunostimulatory molecules. Reactive gliosis and increased expression of proinflammatory cytokines have been demonstrated in old transgenic mice with a model of cerebral amyloid deposition (Birch et al., 2014). To test whether linalool has an immunomodulatory effect on 3xTg-AD mice, we examined astrogliosis and microgliosis by evaluating GFAP and Iba1 immunoreactivity, respectively. Our data showed a significant increase in GFAP immunoreactivity in 3xTg-AD mice compared to the Non-Tg mice; however, linalool treatment significantly reduced the GFAP immunoreactivity in the CA1 hippocampal area, in the EC and in the amygdala compared to that in 3xTg-AD vehicle-treated mice (Fig. 6 a-e). We did not observe changes in the subiculum (Fig. 6 a, c).

Microglial activation is an AD hallmark associated with amyloidosis and tauopathy (Lee et al., 2013). We found that the linalool-treated 3xTg-AD mice displayed microglial immunoreactivity that was significantly decreased in the CA1 area, in the subiculum and in the amygdala compared to that in the vehicle-treated 3xTg-AD mice (Fig. 7 a-e). However, we did not find changes in the EC (Fig. 7 d). Microglial activation was related to βA immunolabeling (Fig. 8 a) and to the hippocampal upregulation of proinflammatory cytokines and the levels of associated marker proteins, such as IL-1β, iNOS, COX-2, and p38 MAPK, which were significantly upregulated in untreated 3xTg-AD mice compared to the Non-Tg group. This inflammatory response was reversed by linalool treatment (Fig. 8 b-e) (p < 0.05 - p < 0.001), confirming previous reports of the anti-inflammatory effects of linalool (Huo et al., 2013; Li et al., 2015).

4. Discussion

Oral administration of the monoterpene linalool ameliorated the histopathological hallmarks of AD and reversed the associated cognitive and emotional deficits in aged triple transgenic AD model mice. Our data suggests that linalool could be a pharmacological therapy for attenuating the neurotoxicity in neurodegenerative diseases. Few studies have reported linalool-mediated neuroprotection. Linalool protects against glucose/serum deprivation (GSD) in PC12 cells (Alinejad et al., 2013) and against acrylamide (ACR)-induced neurotoxicity in Wistar rats, increasing the glutathione (GSH) content while decreasing the ACR-induced lipid peroxidation in rat brain tissue (Mehri et al., 2014). However, other studies show that monoterpenes such as thymol and carvacrol and its derivates, inhibit acetylcholinesterase activity in vitro more strongly than linalool does (Jukic et al., 2007; Perry et al., 2000),
Chapter 2

Linalool reverses neuropathological and behavioral impairments in old triple transgenic Alzheimer’s mice

functions (Campos et al., 2013). Interestingly, our data showed that linalool-treated 3xTg-AD mice exhibited an increased frequency of entry into the open arms, increased head-dipping and reduced grooming and rearing frequencies compared with those of vehicle-treated 3xTg-AD mice. These results suggest reduced anxiety or a “risk assessment” behavior when the mice visit the open arms of the maze (Walf and Frye, 2007), which is unexpected considering that these results were obtained nine days after the final dose of linalool. Our data confirm the results of previous studies reporting that inhaled linalool has anxiolytic properties, increases social interaction, and decreases aggressive behavior (de Almeida et al., 2009; Linck et al., 2010). Although, other study did not report any difference in the number of entries to the open arms using 125 mg/kg linalool (Cline et al., 2008).

Linalool also reduced b-amyloidosis and tauopathy in the hippocampus (CA1, subiculum) and amygdala of aged 3xTg-AD linalool-treated mice compared to untreated mice. These data represent the first evidence that regular administration of linalool can prevent age-related neuropathological and behavioral impairments in old transgenic Alzheimer’s mice.
Chapter 2

Linalool reverses neuropathological and behavioral impairments in old triple transgenic Alzheimer’s mice

Hyperactivated astrocytes and microglial proliferation accompanies βA deposition in the brains of AD model mice (Birch et al., 2014). In the present study, GFAP and Iba1 immunoreactivity was reversed in aged 3xTg-AD mice by oral treatment with linalool. Moreover, linalool dramatically inhibited the LPS-induced phosphorylation of ERK, JNK, and p38 in RAW 264.7 cells (Huo et al., 2013). Linalool also has antioxidant properties and shows protective effects against hydrogen peroxide induced oxidative stress in brain related cognitive impairments and β-amyloid accumulation in 3xTg-AD mice. The decreased b-amyloid level was accompanied by a reduction in β-amyloid 1-40 and 1-42 protein levels. These data are supported by studies, where a mixture of linalool and the monoterpene 2,3,4,4-tetramethyl-5-methylenecyclopent-2-enone led to a significant improvement in the reduction in brain-soluble Aβ 40 (Videira et al., 2014). Linalool is able to cross the blood-brain barrier (Cheng et al., 2015); however, the exact molecular mechanism of the linalool-mediated reduction in β-amyloid needs further study. Tauopathy is detected in pyramidal neurons in CA1 at 15 months of age (Oddo et al., 2003), and in our homozygous mouse colony, it is strongly detected at 18 months of age (Castro-Alvarez et al., 2014). Tauopathy is associated with degenerative symptoms, including significant deficits in hippocampus-dependent cognitive task performance. However, we did not detect immunoreactivity in the EC, which is consistent with some (Mastrangelo and Bowers, 2008; Sabogal-Guaqueta et al., 2015) but not all (Khan et al., 2014) previous studies.
tissue (Celik and Ozkaya, 2002), which together could lead to fewer β-amyloid plaques and reduced tauopathy. Together, these findings suggest that monoterpenes, such as linalool, or the essential oils of several aromatic plants rich in this compound could be beneficial for AD patients or could be used as a chemical basis for the further development novel drugs to treat tauopathies.

5. Conclusion

In summary, our findings suggest that oral administration of linalool at an advanced stage of AD in 3xTg-AD model mice reversed the histopathological hallmarks of AD and restored cognitive and emotional functions. Thus, linalool may be a good candidate for further preclinical studies and future translational studies on AD.

Acknowledgments

The authors thank the Cellular and Molecular Neurobiology Area of the Neuroscience Group of Antioquia, the Group of Bioactive Substances, Professor Jose Ramirez from the Group of Immunomodulation of University of Antioquia and Professor Mariol Lamprea from the Neuroscience Laboratory at National University of Colombia for their scientific and technical support during the experiments. This research was funded by grants from COLCIENCIAS # 11565740581 (GPC-G), CODI University of Antioquia, Young Investigator Programme 2011e2012 Colciencias (AMS-G) and Project 1 R01 AG029802-01 NIA/NIH, Subcontract 2011e2012 (GPC-G). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

References


Linalool reverses neuropathological and behavioral impairments in old triple transgenic Alzheimer’s mice

Chapter 2


