

Original Article

Decrease of Auditory Evoked Delta, Alpha and Beta Oscillatory Responses in D-galactose Induced Aging Model: Effects of Rosmarinic Acid



Deniz Kantar Gok*, Enis Hidisoglu, Hakan Er, Alev Duygu Acun, Piraye Yargıoğlu

Department of Biophysics, Faculty of Medicine, Akdeniz University, Arapsuyu, 07070 Antalya, Turkey

ARTICLE INFO

Article history:

Received 10 October 2017

Received in revised form

18 December 2017

Accepted 17 January 2018

Available online 2 March 2018

Keywords:

D-galactose,

aging,

rosmarinic acid,

auditory evoked oscillations,

lipid peroxidation

SUMMARY

Background: Age-related hearing impairment is one of the most common complaints among older people. It was reported that central neural processing deficits contribute this deficit and improving central auditory function might be beneficial for cognitive functions in elderly. In the present study, we examined the effect of rosmarinic acid (RA) on auditory evoked oscillations and lipid peroxidation in D-galactose induced rat aging model.

Methods: Wistar rats were randomly divided into four groups: sham (S); RA-treated (R); D-galactose-treated (DG); D-galactose + RA-treated (DGR). After eight weeks period, central auditory functions were evaluated by measuring the auditory evoked oscillations over temporal cortex. Thiobarbituric acid reactive substances (TBARS) assay was used to quantify lipid peroxidation levels of the temporal cortex. **Results:** D-galactose treated rats exhibited attenuated auditory evoked delta, alpha and beta responses. Moreover, increased lipid peroxidation levels were detected in the D-galactose treated rats. Eight weeks RA (50 mg/kg) treatment significantly improved oscillatory alterations and lipid peroxidation as compared to DG group.

Conclusion: Thus, present study shows D-galactose induced oscillatory changes in auditory processing and highlights the protective effect of RA against D-galactose induced changes in auditory evoked oscillations and lipid peroxidation.

Copyright © 2018, Taiwan Society of Geriatric Emergency & Critical Care Medicine. Published by Elsevier Taiwan LLC. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

1. Introduction

Aging is a slow and progressive biological process related with complex physiological and biochemical alterations. Although the exact cause of aging is not known, researches indicated that oxidative damage caused by free radicals is an important contributor of aging process.^{1,2} It is well known that brain is particularly vulnerable to oxidative stress because of its high content of polyunsaturated fatty acids, high metabolic rate and low antioxidant defense. The accumulation of free radicals in aging progressively damages functional macromolecules and might therefore be responsible for the age-related dysfunctions and development of degenerative diseases.³ In addition, oxidative stress plays a certain role in the pathology of age-related hearing

impairment (ARHI) which is the most common sensory disorder in the elderly.⁴ ARHI includes the reduction of hearing sensitivity and perceptual difficulties in noisy environment. Although one component of hearing impairment is partly related to peripheral deficit, recent studies concluded that central auditory dysfunction is a prominent component of presbycusis in aging.^{5,6} Electroencephalography (EEG) studies investigating the auditory functions in elderly reported a decrement in the amplitude of ERP components, P300 and N200, and increment in their latencies.^{7,8} On the other hand, there is only a few studies showing the changes in spectral EEG markers.

Natural aging has been experimentally modeled by the chronic administration of D-galactose (D-gal). Since oxidative stress is suggested as one of the main mechanisms of naturally aging, D-gal aging model has been frequently used to study the mechanisms of brain aging and antiaging pharmacology studies.^{9,10} The key mechanism of this animal model is induction of oxidative stress in the course of D-gal metabolism that may account for the

* Corresponding author.

E-mail address: dkantar@akdeniz.edu.tr (D. Kantar Gok).

acceleration of aging.¹¹ Various studies have showed that long term D-gal exposure lead to impairment in cognition, antioxidant system,¹¹ mitochondrial function,¹² calcium homeostasis¹³ and cause apoptosis¹⁴ in the brain. For the sensory system, a study has previously used D-gal to produce a mimetic aging effect in the auditory system and measured the auditory brainstem response (ABR) and middle latency response (MLR) to evaluate central auditory functions in rats.¹⁵ They showed a significant delay in the ABR and MLR latencies. However, the effects of D-gal on the auditory evoked oscillatory dynamics remain poorly understood. In the current work, our first aim is to determine the effects of D-gal -induced aging on simple auditory processing as reflected by auditory evoked EEG oscillations in rats.

In the recent years, naturel compounds with low toxic properties have been widely proposed to used as an alternative agents for the prevention and treatment of various diseases. Rosmarinic acid (RA) is a polyphenolic compound that has been shown to possess many biological activities such as antioxidant,¹⁶ anti-apoptotic¹⁷ and neuroprotective¹⁸ activities. Previous studies demonstrated that the RA is a potent antioxidant by improving antioxidant defense in addition to its direct interaction with free radicals.¹⁶ However, as far as we know, there is no study examining the effects of RA on auditory functions in aging.

The purpose of the present study was to investigate possible protective effect of RA on auditory evoked oscillations in the D-gal injected rats. To date, there have been no studies investigating the effect of RA on oscillatory dynamics of auditory processing. In order to evaluate oxidative cell injury, thiobarbituric acid reactive substances (TBARS) levels of the brain tissue were determined in the present research.

2. Methods

2.1. Animals

All experiments were approved by the Akdeniz University Animal Care and Use Committee and were performed in accordance with the European Community directive. Thirty-two Wistar rats, aged three months, were used. Animals were housed in stainless steel cages in groups of 4 rats per cage at standard conditions ($24 \pm 2^\circ\text{C}$ and $50 \pm 5\%$ humidity) with 12 h light-dark cycle and given food and water ad libitum. The experiments were performed between 9:00 and 17:00. Rats were randomly divided into four groups ($n = 8$ for each): Group 1: rats treated with saline (i.p. and gavage) (S); Group 2: rats treated with saline (i.p.) and RA (gavage) (R); Group 3: rats treated with D-gal (i.p.) and saline (gavage) (DG); Group 4: rats treated concomitantly with D-gal (i.p.) and RA (gavage) (DGR). D-gal (Sigma-Aldrich, St. Louis, MO, USA; 80 mg/kg/day, 80 mg of D-gal dissolved in 0.9% saline solution, to a total volume of 1 ml) was administered by i.p. injection and RA (Carbosynth, San Diego, CA, USA; 50 mg/kg/day, 50 mg of RA dissolved in 0.9% saline solution, to a total volume of 1 ml) was given via gavage for eight weeks.

2.2. AEP recordings

AEPs were recorded between 09:00 am and 02:00 p.m. Rats were anesthetized (24 g/100 ml) with intraperitoneal injections of urethane (1.2 g/kg, Sigma-Aldrich, St Louis, MO, USA). The head of the anesthetized animal was attached to the standard stereotaxic frame and four small holes (1.5 mm diameter) were drilled for the placement of the stainless steel electrodes. Recording electrodes were placed bilaterally on temporal cortices and reference and ground electrodes were placed on cerebellar skull. The rats were confirmed to have normal external auditory canal and tympanic

membranes. The anesthetized animal was moved into a sound-attenuated recording room. Mean background noise level of the recording room measured 46 dB with a sound level meter (Testo 816 Sound Level Meter, Germany).

The EEG signal was amplified (Brainamp EEG/EP Amplifier, Brain Products, Munich, Germany), band-pass filtered (0.1–300 Hz) and digitized at a 1000 Hz sampling rate (Brainvision Recorder, Brain Products, Munich, Germany). AEPs were recorded using tones of 2000 Hz at the 85 dB SLP. A short inter-stimulus interval (ISI) of 500 ms was used. The duration of the tones was 50 ms and the tones were presented through a loudspeaker at a distance of 15 cm from the ear of the rat. The EEG data were processed in 500 ms epochs. Data were filtered (0.1–150 Hz) and baseline corrected. The averaging of 500 responses was performed with a BrainVision Analyzer (Brain Products GmbH). The data were digitally filtered in the delta (0.5–3.5 Hz), alpha (8–15 Hz), and beta (15–30 Hz) frequency ranges. Subsequently, we measured the maximum peak-to-peak amplitudes for each rat's averaged response in terms of microvolts. Then, the digital FFT-based power spectrum analysis was performed (10% Hanning windowing function was evaluated in order to calculate the delta, alpha and beta frequency power).

2.3. Tissue preparation

Animals were anesthetized with the diethyl ether and sacrificed by exsanguination via cardiac puncture. Brain tissue was removed immediately. All tissues were rapidly sonicated in a thermally regulated sonicator (Branson Sonifier 250, G. Heinemann Ultraschall-und Labortechnik, Germany) for 1 min. Sonicated samples were centrifuged and supernatant of centrifuged samples was used for the assay of TBARS measurements.

2.4. TBARS assay

Levels of TBARS were measured by a fluorimetric method described by Wasowicz et al. (1993),¹⁹ using 1,1,3,3-tetraethoxypropane as a standard. Tissue samples were introduced into a tube containing 29 mmol/l thiobarbituric acid in acetic acid (8.75 mol/l), and placed in a water bath and heated for 1 h at $95\text{--}100^\circ\text{C}$. After samples were cooled, 25 ml of 5 M HCl was added and reaction mixture was extracted by agitation for 5 min with 3.5 ml n-butanol. After centrifugation, butanol phase was separated and fluorescence of the butanol extract was measured in a spectrofluorometer (Shimadzu RF-5500, Kyoto, Japan) using wavelengths of 525 nm for excitation, and 547 nm for emission.

2.5. Determination of protein

Protein concentrations in brain tissues were spectrophotometrically measured (Shimadzu RF-5500, Kyoto, Japan) by a protein assay reagent kit (Pierce, Rockford, IL) via a modified Bradford method.²⁰ Bovine serum albumin was used as a standard.

2.6. Statistical analysis

The statistical analysis of the obtained data was performed by SPSS (SPSS 18.0, SPSS Inc., Chicago, IL) software for Windows. Statistical comparisons between groups were performed by using the analysis of variance test and post-hoc Tukey's test.

3. Results

Fig. 1A shows the grand averages of auditory evoked delta oscillations for the temporal electrode for all groups. Delta-band

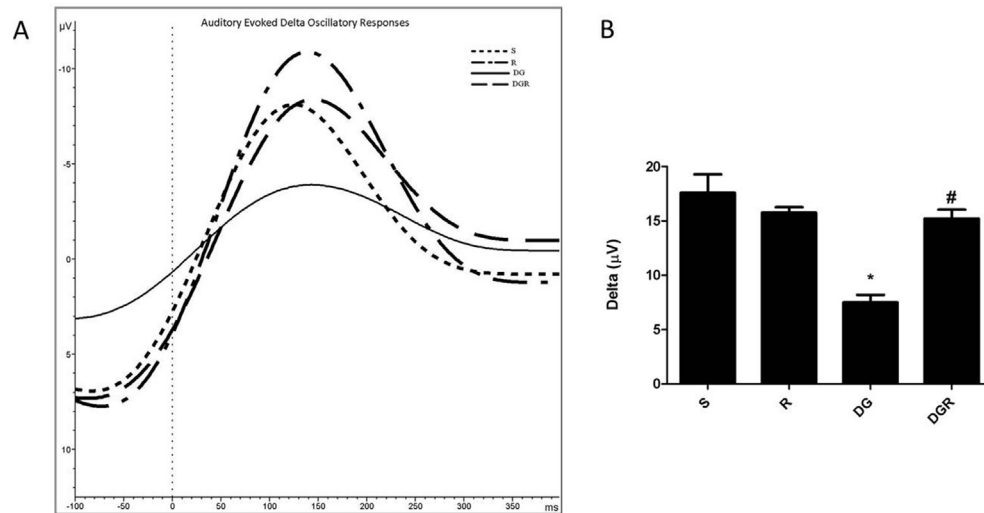


Fig. 1. A: Grand average of auditory evoked delta oscillations (0.5–3.5 Hz) in all experimental groups. B: The means and standard errors of auditory evoked delta oscillations. Results are presented as mean \pm SEM, $n = 8$ for each group (*significant vs. S group; #significant vs. DG group).

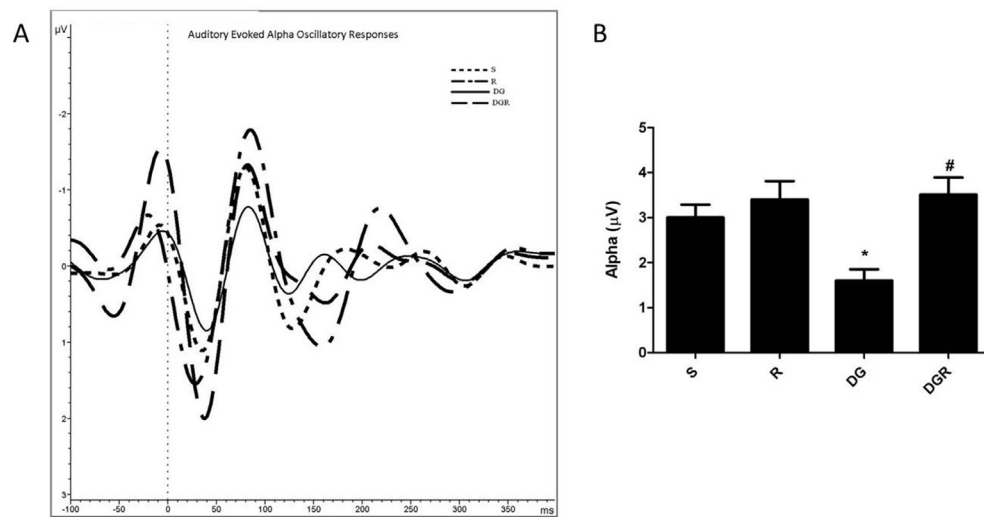


Fig. 2. A: Grand average of auditory evoked alpha oscillations (8–15 Hz) in all experimental groups. B: The means and standard errors of auditory evoked alpha oscillations. Results are presented as mean \pm SEM, $n = 8$ for each group (*significant vs. S group; #significant vs. DG group).

power spectrum values of all groups are given in Fig. 4A. In the present study, there was a significant difference between group in terms of peak-to-peak auditory evoked delta oscillations [$F_{3,31} = 27.66$, $p < 0.01$] and delta-band power [$F_{3,31} = 6.67$, $p < 0.05$]. In post-hoc comparisons, it was found that the DG group had significantly lower peak-to-peak amplitudes of delta oscillatory responses and delta-band power compared with the sham group over temporal locations ($p < 0.05$). The delta amplitudes and power were significantly larger in the DGR group than the DG group ($p < 0.05$). Fig. 1B shows the histogram of peak-to-peak amplitudes of delta oscillatory responses of all groups.

Fig. 2A shows the grand averages of auditory evoked alpha oscillations for the temporal electrodes for all groups. Alpha-band power spectrum values of all groups are given in Fig. 4B. In the present study, there was a significant difference between group in terms of peak-to-peak auditory evoked alpha oscillations [$F_{3,31} = 6.96$, $p < 0.01$] and alpha-band power [$F_{3,31} = 12.97$, $p < 0.01$]. In post-hoc comparisons, it was found that the DG group had significantly lower peak-to-peak amplitudes of alpha

oscillatory responses and alpha-band power compared with the sham group over temporal locations ($p < 0.01$). The alpha amplitudes and power were significantly larger in the DGR group than the DG group ($p < 0.05$). Fig. 2B shows the histogram of peak-to-peak amplitudes of alpha oscillatory responses of all groups.

Fig. 3A shows the grand averages of auditory evoked beta oscillations for the temporal electrodes of all groups. Beta-band power spectrum values of all groups are given in Fig. 4C. There was a significant difference among groups for peak-to-peak amplitudes of auditory evoked beta oscillations [$F_{3,31} = 7.049$, $p < 0.01$] and beta-band power [$F_{3,31} = 14.69$, $p < 0.01$]. Post-hoc comparisons revealed that peak-to-peak amplitudes of beta oscillations and beta-band power were significantly lower for the DG group over the sham group at temporal locations ($p < 0.01$). Further, beta amplitudes and power were significantly elevated in the DGR group versus the DG group ($p < 0.05$). Fig. 3B shows the histogram of peak-to-peak amplitudes of beta oscillatory responses of all groups.

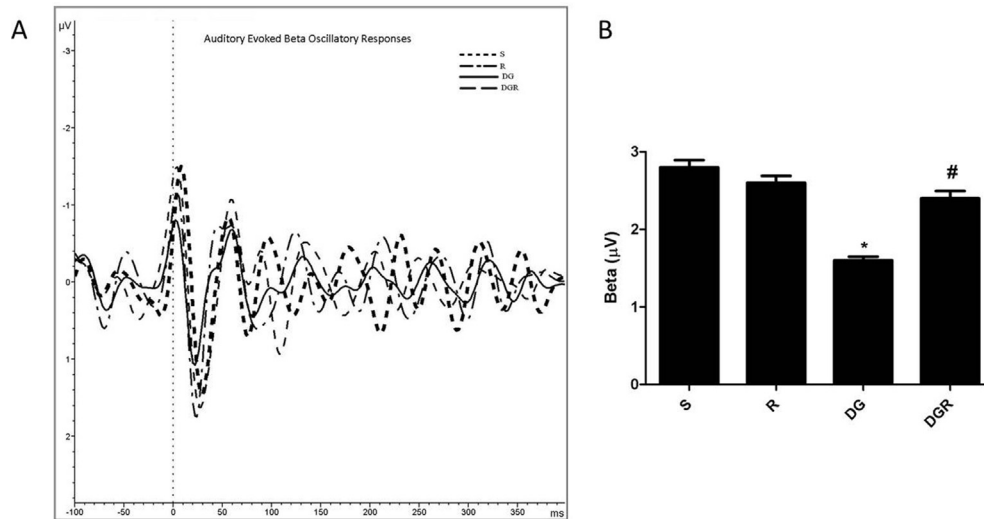


Fig. 3. A: Grand average of auditory evoked beta oscillations (15–30 Hz) in all experimental groups. B: The means and standard errors of auditory evoked beta oscillations. Results are presented as mean \pm SEM, $n = 8$ for each group (*significant vs. S group; #significant vs. DG group).

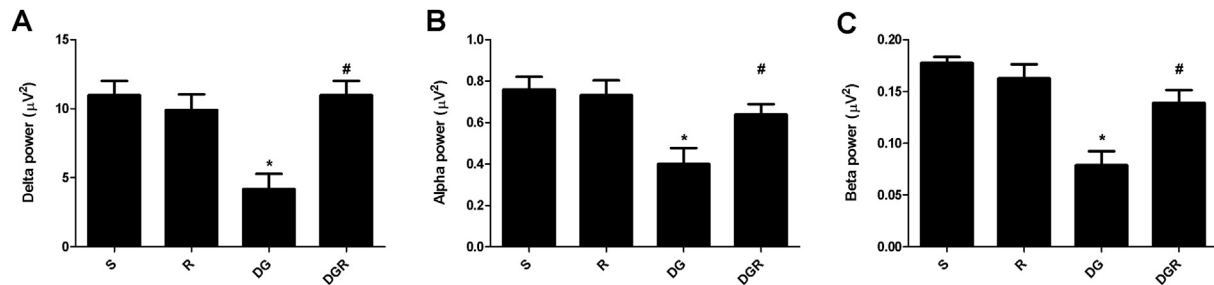


Fig. 4. The means and standard errors of delta, alpha and beta-band power values. Results are presented as mean \pm SEM, $n = 8$ for each group (*significant vs. S group; #significant vs. DG group).

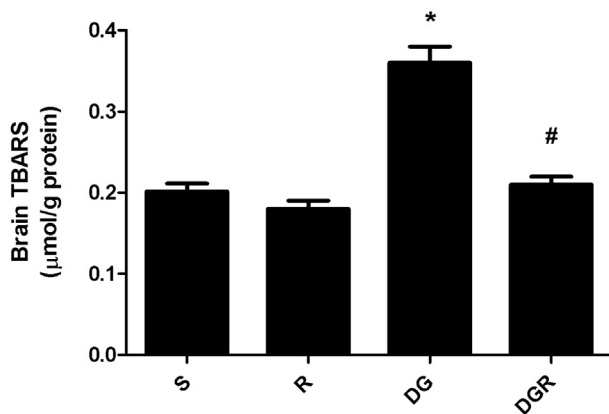


Fig. 5. TBARS levels of the temporal cortex of all experimental groups. Results are presented as mean \pm SEM, $n = 8$ for each group.

Lipid peroxidation was measured as the amount of TBARS. TBARS values of brain tissues of all experimental groups are given in Fig. 5. There was a statistically significant difference between groups [$F_{3,31} = 34.70$, $p < 0.001$]. Brain TBARS levels were significantly increased in the DG group with respect to the Sham group ($p < 0.001$). Further TBARS levels were significantly decreased in the DGR group versus the DG group ($p < 0.01$). No significant difference was observed in TBARS levels in the R group versus the Sham group.

4. Discussion

ARHI, which is characterized with difficulty in speech understanding, is a prominent problem in elderly.⁴ It is known that ARHI has also central component beside peripheral contribution. Because the established link between ARHI with late life cognitive disorders, improving central auditory function with an appropriate treatment might be beneficial for cognitive functions in elderly.^{5,6} Increment of oxidative stress is the main point in the free radical theory of aging. In this context, various antioxidants are widely studied to develop efficient antiaging therapies. Hence, as a known potent antioxidant polyphenol,²¹ we investigated the effect of RA on central auditory functions by examining auditory evoked oscillations in D-gal-injected rats. To the best of our knowledge, there have been no studies done on the effects of D-gal and RA treatment to auditory evoked oscillations at different frequency bands.

Sensory evoked oscillations generates following the presentation of a pure sensory stimulus. A simple auditory sensory stimulus evokes predominantly the function of auditory sensory circuits, and sensory evoked oscillations reflect sensory processes. Therefore, in the current study, we have examined peak-to-peak amplitudes and power of evoked oscillations to determine the altered dynamics in the sensory system.

In the present study, D-gal treated rats showed significantly lower sensory evoked delta responses than sham group rats at temporal locations. Our result is in agreement with an earlier report showing decrement in delta oscillatory responses during visual oddball paradigm in aging²²; even though event related responses

reflect both sensory and cognitive networks. Delta oscillations are generated from pyramidal neurons' long-lasting hyperpolarization and thalamocortical currents. Previous reports have indicated that delta oscillations reflect long distance synchronization in the network.²³ Dysfunction in certain networks might be related with diverse factors in subcellular, cellular or tissue level (e.g., synaptic transmission, axonal transfer, myelination), which can interfere with connectivity.^{24,25} Thus, it could be concluded that decrement in evoked delta synchronization could be partly related with axonal degeneration and/or cellular damage caused by D-gal-induced oxidative stress. This view is in accordance with previous studies showing that D-gal exposure led to cellular damage evidenced with lipofuscin deposition, synaptic degeneration and mitochondrial dysfunction.^{11,26} In parallel, we found that D-gal-induced oxidative damage in D-gal group which was evident with significant increase in lipid peroxidation level.

Furthermore, we found significant reduction in sensory evoked alpha responses. It was reported that alpha oscillations are mainly generated by cortico-cortical and thalamo-cortical neuronal networks.²⁷ Başar (2012)²⁸ stated that time-locked alpha synchronization in specific cortices during sensory stimulation could be considered a specific phenomenon linked with sensory processing. From this point of view, it could be concluded that neuronal synchronization in alpha band has functional importance for sensory processing. Beside, a study showed that D-gal administration leads to an impairment in auditory processing accompanying with lipid peroxidation and neurodegeneration similar to naturel aging.¹⁵ Previous human studies also concluded that impaired temporal and spectral coding in perception is resulted from age-related loss in neural synchrony in elderly.^{29,30} These findings indicate that alpha desynchronization may involve in the deficiency of auditory processing in D-gal-induced aging model. Moreover, we determined significant reduction in sensory evoked beta responses. The functional role of beta oscillatory responses seems to be less analyzed in comparison to other frequency bands.³¹ Beside other known functional correlates of beta oscillations, such as novelty detection in the auditory system and sensory gating, beta rhythm claimed to be involved in sensory integrative processes. Previous studies indicated that regional resonances in beta and alpha reflect multimodal synchronization between macrocolumns.³² While short-distance synchronization tends to occur at higher frequencies like gamma-band, long-distance synchronization manifests itself in the beta and alpha frequency ranges.^{33,34} So it is conceivable to suggest that D-gal-induced oxidative changes lead to long-distance desynchronization in different dimension of the network. In sum, integrative brain function that requires combined action of multiple oscillations during performance of sensory-cognitive tasks, affected in D-gal aging model.

A growing body of evidence indicates that oxidative damage in degenerative conditions such as lipid peroxidation can be prevented by antioxidant therapies.³⁵ RA is known to be one of the most potent antioxidant among other polyphenols.³⁶ Our current findings are in agreement with our lab and others results which have showed that RA effectively inhibited lipid peroxidation in different experimental designs.^{37,38} To the best of our knowledge, this is the first study investigating the effect of RA on auditory oscillatory dynamics in D-gal-induced changes. We showed that RA administration lead to a significant increment in peak-to-peak amplitudes of delta, alpha and beta oscillations in comparison to DG group. Our results also confirm our recent report showing that RA can efficiently improve brain network activity at least in sensory level. Therefore, it can be concluded that RA diminished the detrimental effects of D-gal on sensory processes, most likely by decreasing the lipid peroxidation. On the other hand, the role of other possible mechanisms of action of

RA, such as reported cholinergic enhancement, cannot be completely excluded in the observed beneficial effects. So, consumption of RA or RA containing naturel compounds as nutritional supplement might prevent ARHI in elderly. In this context, RA, as a potent candidate in the use of naturally occurring antioxidants, could be studied for its therapeutic potential and development of preventive cure for age-related changes in auditory functions.

Conflicts of interest

Authors declare no conflict of interest.

References

- Harman D. Aging: a theory based on free radical and radiation chemistry. *J Gerontol.* 1956;11:298–300.
- Cui H, Kong Y, Zhang H. Oxidative stress, mitochondrial dysfunction, and aging. *J Signal Transduct.* 2012;2012:646354.
- Pereira MD, Ksiazek K, Menezes R. Oxidative stress in neurodegenerative diseases and ageing. *Oxid Med Cell Longev.* 2012;2012:796360.
- Fujimoto C, Yamasoba T. Oxidative stresses and mitochondrial dysfunction in age-related hearing loss. *Oxid Med Cell Longev.* 2014;2014:582849.
- Gates GA, Feeney MP, Mills D. Cross-sectional age-changes of hearing in the elderly. *Ear Hear.* 2008;29:865–874.
- Humes LE, Dubno JR, Gordon-Salant S, et al. Central Presbycusis: a review and evaluation of the evidence. *J Am Acad Audiol.* 2012;23:635–666.
- Goodin DS, Squires KC, Henderson BH, et al. Age-related variations in evoked-potentials to auditory-stimuli in normal human subjects. *Electroencephalogr Clin Neurophysiol.* 1978;44:447–458.
- Bertoli S, Probst R. Lack of standard N2 in elderly participants indicates inhibitory processing deficit. *Neuroreport.* 2005;16:1933–1937.
- Zhu JH, Mu XY, Zeng J, et al. Ginsenoside Rg1 prevents cognitive impairment and Hippocampus senescence in a rat model of D-galactose-induced aging. *PLoS One.* 2014;9. e101291.
- Wang C, He L, Yan M, et al. Effects of polyphenols from pine needles of *Pinus massoniana* on ameliorating cognitive impairment in a D-galactose-induced mouse model. *Age (Dordr).* 2014;36:9676.
- Cui X, Zuo P, Zhang Q, et al. Chronic systemic D-galactose exposure induces memory loss, neurodegeneration, and oxidative damage in mice: protective effects of R-alpha-lipoic acid. *J Neurosci Res.* 2006;84:647–654.
- Long JG, Wang XM, Gao HX, et al. D-galactose toxicity in mice is associated with mitochondrial dysfunction: protecting effects of mitochondrial nutrient R-alpha-lipoic acid. *Biogerontology.* 2007;8:373–381.
- Lu J, Zheng YL, Luo L, et al. Quercetin reverses D-galactose induced neurotoxicity in mouse brain. *Behav Brain Res.* 2006;171:251–260.
- Mao Z, Zheng YL, Zhang YQ, et al. The anti-apoptosis effects of daidzein in the brain of D-Galactose treated mice. *Molecules.* 2007;12:1455–1470.
- Chen B, Zhong Y, Peng W, et al. Age-related changes in the central auditory system: comparison of D-galactose-induced aging rats and naturally aging rats. *Brain Res.* 2010;1344:43–53.
- Ghaffari H, Venkataramana M, Ghassam BJ, et al. Rosmarinic acid mediated neuroprotective effects against H₂O₂-induced neuronal cell damage in N₂A cells. *Life Sci.* 2014;113:7–13.
- Kim DS, Kim HR, Woo ER, et al. Inhibitory effects of rosmarinic acid on adriamycin-induced apoptosis in H9c2 cardiac muscle cells by inhibiting reactive oxygen species and the activations of c-Jun N-terminal kinase and extracellular signal-regulated kinase. *Biochem Pharmacol.* 2005;70:1066–1078.
- Fallarini S, Miglio G, Paoletti T, et al. Clovamide and rosmarinic acid induce neuroprotective effects in in vitro models of neuronal death. *Br J Pharmacol.* 2009;157:1072–1084.
- Wasowicz W, Neve J, Peretz A. Optimized steps in fluorometric determination of thiobarbituric acid-reactive substances in serum: importance of extraction pH and influence of sample preservation and storage. *Clin Chem.* 1993;39:2522–2526.
- Bradford MM. A rapid and sensitive method for the quantitation of microgram quantities of protein utilizing the principle of protein-dye binding. *Anal Biochem.* 1976;72:248–254.
- Petersen M, Simmonds MS. Rosmarinic acid. *Phytochemistry.* 2003;62:121–125.
- Emek-Savas DD, Guntekin B, Yener GG, et al. Decrease of delta oscillatory responses is associated with increased age in healthy elderly. *Int J Psychophysiol.* 2016;103:103–109.
- Bruns A, Eckhorn R. Task-related coupling from high- to low-frequency signals among visual cortical areas in human subdural recordings. *Int J Psychophysiol.* 2004;51:97–116.
- Tkachev D, Mimmack ML, Ryan MM, et al. Oligodendrocyte dysfunction in schizophrenia and bipolar disorder. *Lancet.* 2003;362:798–805.

25. Uranova NA, Vostrikov VM, Orlovskaya DD, et al. Oligodendroglial density in the prefrontal cortex in schizophrenia and mood disorders: a study from the Stanley Neuropathology Consortium. *Schizophr Res.* 2004;67:269–275.
26. Xu XH, Zhao TQ. Effects of puerarin on D-galactose-induced memory deficits in mice. *Acta Pharmacol Sin.* 2002;23:587–590.
27. Dasilva FL. Neural mechanisms underlying brain waves - from neural membranes to networks. *Electroencephalogr Clin Neurophysiol.* 1991;79:81–93.
28. Basar E. A review of alpha activity in integrative brain function: fundamental physiology, sensory coding, cognition and pathology. *Int J Psychophysiol.* 2012;86:1–24.
29. Tremblay KL, Piskosz M, Souza P. Effects of age and age-related hearing loss on the neural representation of speech cues. *Clin Neurophysiol.* 2003;114:1332–1343.
30. Harkrider AW, Plyler PN, Hedrick MS. Effects of age and spectral shaping on perception and neural representation of stop consonant stimuli. *Clin Neurophysiol.* 2005;116:2153–2164.
31. Engel AK, Fries P. Beta-band oscillations—signalling the status quo? *Curr Opin Neurobiol.* 2010;20:156–165.
32. Basar E, Basar-Eroglu C, Karakas S, et al. Oscillatory brain theory: a new trend in neuroscience—The role of oscillatory processes in sensory and cognitive functions. *IEEE Eng Med Biol.* 1999;18:56–66.
33. von Stein A, Chiang C, Konig P. Top-down processing mediated by interareal synchronization. *Proc Natl Acad Sci USA.* 2000;97:14748–14753.
34. Kopell N, Ermentrout GB, Whittington MA, et al. Gamma rhythms and beta rhythms have different synchronization properties. *Proc Natl Acad Sci USA.* 2000;97:1867–1872.
35. Uttara B, Singh AV, Zamboni P, et al. Oxidative stress and neurodegenerative diseases: a review of upstream and downstream antioxidant therapeutic options. *Curr Neuropharmacol.* 2009;7:65–74.
36. Soobrattee MA, Neergheen VS, Luximon-Ramma A, et al. Phenolics as potential antioxidant therapeutic agents: mechanism and actions. *Mutat Res.* 2005;579:200–213.
37. Gao LP, Wei HL, Zhao HS, et al. Antiapoptotic and antioxidant effects of rosmarinic acid in astrocytes. *Pharmazie.* 2005;60:62–65.
38. Gok DK, Ozturk N, Er H, et al. Effects of rosmarinic acid on cognitive and biochemical alterations in ovariectomized rats treated with D-galactose. *Folia Histochem Cytobiol.* 2015;53:283–293.