Neuromodulatory Mechanisms of a Memory Loss-Preventive Effect of Alpha-Lipoic Acid in an Experimental Rat Model of Dementia

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Abstract
This study evaluates some of the neuromodulatory mechanisms of the memory loss preventive effect of alpha-lipoic acid (ALA) in a scopolamine (Sco)-induced rat model of Alzheimer’s disease (AD) type dementia. Our results confirmed that Sco administration induces significant memory impairment, worsens exploratory behaviour and habituation, increases acetylcholinesterase (AChE) activity, and induces pathological monoamine content changes in the prefrontal cortex and hippocampus. ALA administration largely prevented Sco-induced memory impairment. It also improved exploratory behaviour and preserved habituation, and it decreased AChE activity, reversing it to control group levels, and corrected aberrant monoamine levels in the prefrontal cortex and hippocampus. According to the data available, this is the first time that ALA-induced changes in AChE and monoamine levels in the prefrontal cortex and hippocampus (brain structures related to learning and memory) have been demonstrated in a Sco-induced rat model of AD type dementia.

Keywords Alzheimer’s type dementia · Lipoic acid · Neurodegeneration · Acetylcholine esterase · Monoamine · Memory loss

Introduction
Alzheimer’s disease (AD) is the most common form of dementia and is currently ranked as the third leading cause of death, trailing only cardiovascular disease and neoplasia (James et al. 2014a, b). AD is associated with a decline in cognitive function, thinking, remembering, reasoning and behavioural abilities (Huang et al. 2016; Ray et al. 2012). One of its major neuropathological hallmarks is the deposition of amyloid beta (Aβ)-peptide-containing senile plaques and intracellular neurofibrillary tangles in hippocampal and cerebrocortical regions (González-Reyes et al. 2017). Altered calcium homeostasis, increased brain oxidative stress (OS), neuroinflammation and mitochondrial dysfunction contribute to the ongoing pathology (Mancuso et al. 2006). These alterations lead to a progressive reduction in the number of cholinergic neurons and the levels of the neurotransmitter acetylcholine (ACh) (Nordberg and Winblad 1986; Nordberg et al. 1987)—important indicators of AD severity. Pathological changes can also be seen in monoaminergic neurotransmission (D’Amelio and Rossini 2012; Roy et al. 2016; Scheff et al. 2006; Burns et al. 2005), exerting a negative effect on working memory, memory consolidation and retrieval (Sara 2009; Chudasama and Robbins 2004; Sara 2017; Schicknick et al. 2019). Most of the current AD drug therapy aims to increase brain ACh levels, mainly through the use of different AChE inhibitors.

Alpha-lipoic acid (ALA) is a naturally occurring molecule with neuroprotective, anti-inflammatory, metal-chelating and strong antioxidant properties. Data also show that it exerts protective effects on mitochondrial function (Miquel 2002). Its reduced form (dihydrolipoic acid) is responsible for many of its beneficial pharmacological effects, namely acting as a metal chelator, reducing reactive oxygen species (ROS) production (Ferreira et al. 2009) and regenerating other low-molecular-weight antioxidants such as glutathione (GSH), coenzyme Q10, and vitamins A and C (Bilska et al. 2007). Its anti-inflammatory effect is realized via a direct
effect on gene expression or an indirect effect on several cAMP-dependent signal transduction pathways (Bozhokina et al. 2015; Fiedler et al. 2018; Meng et al. 2018; Dinicola et al. 2017). In our previous research we demonstrated an antioxidant and memory-protective effect of ALA in a scopolamine (Sco)-induced rat model of dementia (Tzvetanova et al. 2018). By acting as an antioxidant, and due to its neuromodulatory activity described below, ALA can interfere with and remediate dementia pathogenesis pathways, for example those in AD. There are data demonstrating that patients with mild AD who have been treated with ALA show a slower progression of cognitive impairment (Molz and Schröder 2017; Heneka and O’Banion 2007; Fu et al. 2014). An ability of ALA to affect cholinergic neurotransmission-related cognitive function by increasing ACh production has also been reported (Fava et al. 2013).

The neuromodulatory effect of ALA on brain monoaminergic neurotransmission in neuropathological conditions has not been well studied. Data regarding its ability to affect acetylcholinesterase (AChE)—a fundamental component of cholinergic neurotransmission—are also scarce. It was shown that ALA treatment restored normal levels of AChE that were increased in an aluminium-induced AD rat model (Ahmed 2012). The ability of ALA to increase brain levels of serotonin (Sero), dopamine (DA) and noradrenaline (NA) was demonstrated in an Aβ vaccine-induced AD model in mice (Jesudason et al. 2005).

In light of the above-mentioned findings, this work aims to evaluate some of the complex neuromodulatory mechanisms of the memory loss-preventive effect of ALA in an experimental Sco-induced rat model of AD type dementia.

Materials and Methods

Chemicals

The reagents for the biochemical assay were obtained from Sigma-Aldrich (Germany). Scopolamine hydrobromide was purchased from ACROS Organics and ALA (as Thio gamma® Turbo-Set 600 mg/50 ml solution for injection) from Solupharm GmbH & Co. KG (Germany). All other chemicals were of the highest commercially available purity.

Animals

Adult male Wistar rats weighing 160–180 g were housed three per cage, on a 12 h/12 h light/dark cycle, with ambient temperature measuring 25 ± 3 °C. Food and water were accessible ad libitum. Before commencing the experiment, the rats were given a 5-day habituation period.

Sco-induced Rat Model of AD Type Dementia

A Sco-induced rat model of AD type dementia was achieved by injecting scopolamine hydrobromide 2 mg/kg, intraperitoneally (i.p.), for 11 consecutive days. The dose was selected based on our previous studies (Tzvetanova et al. 2020) as well as on literature data (Lee et al. 2012; Upadhyay et al. 2020; Shivakumar et al. 2014).

Experimental Design

After 5 days of habitation, the rats were randomly divided into the following three groups (numbering 12 per group) and treated for 11 consecutive days: control group (treated with saline 0.5 ml/100 g, i.p.), Sco group (treated with Sco 2 mg/kg i.p.) and Sco+ALA group (treated with Sco 2 mg/kg i.p. and ALA 30 mg/kg i.p.). Sco was dissolved in distilled water ex tempore before each administration. ALA (Thio gamma® Turbo-Set 600 mg/50 ml solution for injection) was diluted with saline to be properly administered. At the 24th hour and on the 12th day after the first administration, the rats were subjected to behavioural assessment (step-through passive avoidance test and hole-board test). Behavioural observation was conducted from 9 a.m. to 12 p.m. One hour after the last test, the animals were euthanized by decapitation under mild CO2 inhalation. Two important brain structures related to memory (prefrontal cortex and hippocampus) were isolated for biochemical analysis.

Behavioural Assessment

Step-through Passive Avoidance Test A step-through passive avoidance test was used to evaluate potential changes in the rats’ short- and long-term memory, by assessing changes in reaction time (Jarvik and Kopp 1967). The apparatus used was composed of two chambers (a darkened and lit one) separated by a guillotine door. During the acquisition phase of the test, in the darkened chamber of the apparatus, the animals were exposed to the action of the aversive stimulus (a 0.1 mA electric shock lasting for 1 s). The initial latency (IL) between placing the animals in the lit chamber and their spontaneous entrance into the darkened chamber was recorded. The animals were then tested at the 24th hour and on the 12th day after the acquisition session using the same paradigm, only without applying the foot-shock. The time to transition from the lit to the darkened chamber was recorded as the step-through latency (STL). When a rat did not enter the dark chamber within 180 s, the latency was recorded as 180 s.
Hole-board Test  The hole-board apparatus consisted of a platform (50 × 50 cm) with 16 symmetrically arranged round holes with a diameter of 3 cm. To evaluate changes in exploratory behaviour, the rats were placed onto the platform and the number of head dips into the holes during a 3-min period were counted (Boissier et al. 1964). To evaluate changes in habituation, the rats were placed onto the platform and the number of head dips into the holes during the first, second and third minutes were counted.

Biochemical Assessment

AChE Activity  AChE activity in rat brain structures was assayed based on Ellman’s method (Ellman et al. 1961), in which the thiocholine produced by the action of AChE forms a yellow colour with 5,5′-dithiobis(2-nitrobenzoic acid) (DTNB). First, 10% tissue homogenate, prepared in 0.1 M phosphate buffer (pH = 8; 1000 rpm), was centrifuged at 4500 rpm for 10 min, after which 100 µl of supernatant was incubated with Ellman’s reagent, 0.01 M DTNB, 0.1 M phosphate buffer and 0.075 M freshly prepared acetylthiocholine iodide. Next, 500 µl of the reaction mixture was injected into a semi-auto chemistry analyser and reaction kinetics were monitored for 3 min at 405 nm. Values are expressed as U/ml/mg protein. Protein content was measured by the method of Lowry et al. (1951).

Biogenic Amine Concentration Measurement  The concentrations of biogenic amines—NA, DA and Sero—were determined by a fluorescence reaction in tissue homogenates (Jacobowitz and Richardson 1978). NA and DA were extracted into a 0.1 M phosphate buffer and Sero into 0.1 N HCl. For the NA and DA fluorescence reaction, ethylenediaminetetraacetic acid (EDTA), iodide solution, alkaline sulphite and 5 N CH3COOH were added, whereas for the Sero fluorescence reaction, o-phthalaldehyde (OPT) was added. Fluorescence was determined at λ = 385/485 nm for NA, λ = 320/385 nm for DA and λ = 360/470 nm for Sero, respectively. Monoamine fluorescence levels were then calculated based upon standard solution fluorescence and expressed as nanograms per gram of fresh tissue.

Statistical Analysis

The results are expressed as mean ± SEM. Student’s t test was used for statistical analysis of unpaired data. A multiple-sample comparison was applied to test the differences between groups (one-way analysis of variance [ANOVA] and Dunnett’s as the post hoc comparison test, two-way ANOVA and Tukey’s multiple comparisons test). Statistical analysis was performed using GraphPad Prism. A value of \( P < 0.05 \) was taken to indicate a statistically significant difference. Artwork was created using the GraphPad Prism 8 graphics program.

Results

Effect of ALA on Learning and Memory of Dementia Rats

The alterations in learning and memory performance of rats with Sco-induced dementia were evaluated by measuring the latency in entering a dark compartment in a step-through passive avoidance test (Fig. 1). Our results showed that 11 consecutive days of Sco treatment affected both the
short- and long-term memory of the animals, manifesting as decreased STL. The reduction in reaction time latency was 64% \((P < 0.01, n = 6)\) at the 24th hour and 73% \((P < 0.05, n = 12)\) on the 12th day versus controls.

Multiple ALA injections restored Sco-impaired long-term memory. After 11 consecutive days of simultaneously treatment, STL in the Sco+ALA group was increased by 69% \((P < 0.05, n = 12)\) as compared to the Sco group.

**Effect of ALA on Rat Exploratory Activity of Dementia Rats**

The changes in exploratory activity (Fig. 2a) and habituation pattern (Fig. 2b) of the animals with experimental dementia were assessed by the hole-board test. Eleven days of Sco administration resulted in a significant reduction in the number of head dips, by 91.6% \((P < 0.001, n = 12)\) as compared to the control—an indication of exploratory behaviour deterioration. The habituation pattern was also negatively affected. Placed in an unfamiliar environment, the Sco-treated animals did not change their response to the stimulus within the observed period of 3 min—a sign of a memory impairment effect.

In the ALA+Sco group, the total number of head dips was increased in comparison to the Sco group, though the difference was nonsignificant and the habituation pattern was preserved. These results indicate a positive effect of ALA on exploratory activity and memory function.

**Biochemical Evaluation**

**Effect of ALA on Brain AChE Activity of Dementia Rats**

The effect of ALA on the brain AChE activity of animals with experimental dementia is demonstrated in Fig. 3. Eleven consecutive Sco injections increased the levels of AChE in the prefrontal cortex by 25% \((P < 0.05, n = 6)\) and in the hippocampus by 40% \((P < 0.05, n = 6)\), as compared to the controls. Our results showed that multiple ALA injections restored AChE activity close to control levels in both brain structures. In the hippocampus of Sco+ALA-treated animals, the AChE activity was decreased by 44% \((P < 0.05, n = 6)\), in comparison to the Sco-treated group.

These results suggest that the protective effect of ALA on memory could be partly due to AChE inhibition.

**Neuromodulatory Activity of ALA on Brain Monoamine Levels of Dementia Rats**

The neuromodulatory capacity of ALA in the prefrontal cortex and hippocampus of the animals with experimental dementia is demonstrated in Fig. 4. Eleven consecutive days of Sco treatment decreased DA levels by 51% \((P < 0.001, n = 6)\), produced a nonsignificant change in NA levels and increased Sero levels by 186% \((P < 0.001, n = 6)\), as compared at \(* P < 0.05, ** P < 0.01, *** P < 0.001\). Hashtag above the bars indicates a significant difference in number of head dips between the Sco+ALA and Sco groups at \# P < 0.05. Statistical analysis was performed by one-way ANOVA with Dunnett’s post hoc comparison test, and by two-way ANOVA with Tukey’s multiple comparisons test, graphics program: GraphPad Prism 8.
to the control. In the hippocampus, the levels of DA and NA were decreased by 84% \((P<0.01; \ P<0.001, \ n=6)\) and those of Sero by 45% (Fig. 4).

In the Sco+ALA group, ALA administration decreased Sero levels in the prefrontal cortex by 86% \((P<0.001, \ n=6)\), but did not significantly change

Fig. 3 Effect of ALA on AChE activity in prefrontal cortex and hippocampus in Sco-induced rat model of dementia. Results are expressed as mean values ± SEM \((n=6\) animals per group). Asterisk above the bars indicates a significant difference in AChE activity between the Sco and control group at \(^*P<0.05\), \(^{***}P<0.001\).

Fig. 4 Effect of ALA on monoamine levels in the prefrontal cortex and hippocampus in Sco-induced rat model of dementia. Results are expressed as mean values ± SEM \((n=6\) animals per group). Asterisk above bars indicates a significant difference in monoamine levels between the Sco and control group at \(^{**}P<0.01\), \(^{***}P<0.001\).
those of DA or NA as compared to the Sco group. In the hippocampus, the levels of DA, NA and Sero were increased by 367\% (P < 0.05, n = 6), 700\% (P < 0.001, n = 6) and 179\% (P < 0.05, n = 6), respectively, versus the Sco group.

Discussion

AD is a progressive disorder, mainly affecting the cholinergic neurons in the prefrontal cortex and the hippocampus (Arendt 2012; Serrano-Pozo et al. 2011). Cardinal symptoms of the disease include a decline in memory and other cognitive skills, and alterations in mood, orientation, and behaviour—ultimately leading to a complete disintegration of the personality and an untimely death.

In the present study we endeavoured to expand the available information regarding the complex mechanisms of the action of ALA and its effects on cognitive function. We investigated a possible connection between the ability of ALA to improve learning and memory, AChE activity and monoamine levels in the prefrontal cortex and the hippocampus of rats with Sco-induced dementia.

As a competitive muscarinic receptor antagonist, Sco has been traditionally used in the field of neuropsychopharmacology to induce experimental dementia (Ebert and Kirch 1998; Flood and Cherkin 1986). It can cause cognitive decline very similar to that observed in AD disease (Spinks and Wasiak 2011; El-Sherbiny et al. 2003; Goverdhan et al. 2012; Tzvetanova et al. 2018) and it can serve as a useful tool for the investigation of learning and memory impairments.

In the present study, Sco-induced cognitive deficits were demonstrated using two behavioural tests: step-through passive avoidance and hole-board tests. By using the step-through passive avoidance test, alterations in learning and memory performance were evaluated by observing changes in STL. This is a fear-conditioning test that creates a conflict in the rat’s mind—between the instinct to prefer the dark compartment of the apparatus and the fear of the electrical current they would receive there (Romanski and LeDoux 1993).

We found that prolonged ALA administration in the Sco+ALA group had a preventive effect on disruption of long-term memory by Sco. This is in line with our previous studies (Dragomanova et al. 2016; Tzvetanova et al. 2018), in which a correlation between the memory-improving effect of ALA and its strong antioxidant effect was demonstrated.

The memory-improving effect of ALA demonstrated in the step-through passive avoidance test was also confirmed by the hole-board test. For a period of 3 min, we observed differences in the total number of head dips (an indicator of exploratory behaviour deterioration) and changes in habituation patterns between the groups. We should note the significance of these habituation changes as a non-associative test for learning in animals placed in an unfamiliar environment. Our experiments demonstrated that multiple ALA injections prevented Sco-induced impairment of exploratory behaviour and habituation of the experimental animals.

It is a well-established fact that cognitive function is directly dependent on the normal physiology of the cholinergic system—in the prefrontal cortex, the hippocampus and some parts of the striatum (Braak and Braak 1996). The loss of neurons in these brain areas is one of the main pathological features of AD, leading to a severe diminishment of synaptic cleft acetylcholine (ACh) concentration (Bartus et al. 1982). One way to increase this concentration is by inhibiting the activity of the AChE—an enzyme responsible for the hydrolysis of ACh (Ballard et al. 2005). The ability of ALA to increase cholinergic activity in certain brain areas is well documented in the literature (Ahmed 2012). For example, it was shown that ALA treatment restored increased AChE activity in an aluminium-induced rat model of AD (Ahmed 2012). However, until now, there were no available data for the effect of ALA on AChE activity in a Sco-induced rat model of dementia. In the present study, 11 consecutive days of Sco administration disrupted brain cholinergic activity, causing an increase in AChE activity in the prefrontal cortex and the hippocampus. This was accompanied by memory impairment, as demonstrated by the behavioural assessment. These findings are in line with the findings of Zaki et al. (2014), Hasselmo (2006) and Francis et al. (1999). ALA administration in turn restored Sco-increased AChE activity to normal levels and can explain (albeit partially) the observed memory improvement effect.

However, pathological brain changes in AD not only affect cholinergic neurotransmission, but also damage NA, DA, Sero and glutamatergic neurotransmission (D’Amelio and Rossini 2012; Roy et al. 2016; Scheff et al. 2006; Burns et al. 2005).

Our results showed that Sco administration resulted in changes in the brain levels of all the above-mentioned neurotransmitters when compared to controls. In the prefrontal cortex, DA levels were decreased, Sero levels were increased, and NA levels were not significantly affected. In the hippocampus, the levels of all the measured neurotransmitters were decreased in comparison to the controls.

To our knowledge, this is the first study to investigate the potential of ALA in modulating brain monoamine content in a rat model of Sco-induced dementia. Given the relationship between cerebral monoaminergic neurotransmission, working memory, memory consolidation and memory retrieval (Sara 2009, 2017; Schicknick et al. 2019), we believe that the ability of ALA to induce changes in brain DA, NA and Sero levels can partly explain its beneficial effects on memory.
Conclusion

We can conclude that the memory-improving effect of ALA is related to its neuromodulatory capacity to affect the cholinergic and monoaminergic systems in two brain areas related to memory—the prefrontal cortex and hippocampus. According to the data available, this is the first time that ALA-induced changes in AChE and monoamine levels in these brain areas have been demonstrated in a Sco-induced rat model of dementia. Future investigations are needed to clarify the clinical significance of these findings.

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Author Contributions Conception and design [Lyubka Tancheva], [Maria Lazarova], and [Rumen Nikolov]. Material preparation, data collection and analysis were performed by [L. Tancheva], [M. Lazarova], [Hristian Staykov], [Yozljam Hassanova], [Miroslava Stefanova]. The first draft of the manuscript was written by [M. Lazarova] and all authors comment on previous version of the manuscript. All authors read and approved the final manuscript.

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Availability of Data and Materials The material used during the present study is available from the corresponding author on reasonable request.

Data Availability Statement The authors confirm that all data generated or analysed during this study are included in this published article.

Declarations

Ethics Approval and Consent to Participate The experiments have been performed strictly according to the national regulations and European Communities Council Directive (86/609/EEC) also Principles of laboratory animal care (NIH publication No. 85-23) concerning the protection of animals used for scientific and experimental purposes. All efforts and study design was made with purpose to minimize number of the animals and their suffering.

Consent for Publication The authors declare their consent for publication.

Competing Interests The authors have no relevant financial or non-financial interests to disclose.

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